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Instituto de Biociências de Botucatu

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Farmacomagnetografia de sistemas gastrorretentivos flutuantes *in vivo* em diferentes estados prandiais avaliados por Biosusceptometria AC.

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GUSTAVO SERAFIM RODRIGUES

Tese de Doutorado apresentada ao Instituto de Biociências, Universidade Estadual Paulista "Júlio de Mesquita Filho", Campus de Botucatu, para obtenção do título de Doutor em Ciências Biomoleculares e Farmacológicas.

Orientador: Prof. Titular Dr. José Ricardo de Arruda Miranda

Coorientador: Profª. Dra. Priscileila Corelato Ferrari

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LISTA DE ABREVIAÇÕES

TRG - Tempo de retenção gástrica

BAC - Biosusceptometria de corrente alternada

HPMC - Hidroxipropilmetilcelulose

FLT - Floating lag time

GRT - Gastric retention time

OCTT - Orocecal transit time

SITT - Small intestinal transit time

Tmax - Tempo para atingir a concentração plasmática máxima

$AUC_{0-\infty}$ - Área sob a curva

CMM - Complexo motor migratório

TGI - Trato gastrintestinal

FFLM - Formas farmacêuticas para liberação modificada

GRDDS – Gastro Retentive Drug Delivery Systems

HBS - Hydrodynamically Balanced Systems

SQUID - Dispositivos supercondutores de interferência quântica

AMR - Sensores anisotrópicos magnetorresistivos

MRI - Ressonância magnética

RESUMO

O presente estudo teve como objetivo o desenvolvimento, caracterização e avaliação de um comprimido magnético flutuante capaz de prolongar o tempo de retenção gástrica (TRG), otimizando a absorção e a biodisponibilidade de fármacos cuja janela terapêutica está localizada na porção proximal do trato gastrointestinal. A proposta se baseou na aplicação da técnica de Biosusceptometria de Corrente Alternada (BAC) como ferramenta não invasiva para monitoramento em tempo real do comportamento gastrointestinal da forma farmacêutica, permitindo a correlação de parâmetros farmacotécnicos (in vitro), parâmetros de trânsito e farmacocinéticos (farmacomagnetografia/ in vivo). A formulação desenvolvida consistiu em uma matriz polimérica contendo hidroxipropilmetilcelulose (HPMC), agente efervescente gerador de gás (bicarbonato de sódio) e ferrita de manganês como marcador magnético. Foram conduzidos estudos in vitro com o objetivo de avaliar a influência de variáveis fisiológicas simuladas (viscosidade/ pressão intragástrica) no desempenho da forma farmacêutica. Para isso, foram realizados ensaios em meios com diferentes viscosidades (1, 50, 120 e 320 mPa·s) e sob diferentes pressões intragástricas (760, 910 e 1060 mmHg), representando condições do estômago em jejum e alimentado. Foram avaliados parâmetros como tempo de início de flutuação (Floating Lag Time – FLT), tempo de retenção gástrica (Gastric Retention Time – GRT), tempo de trânsito orocecal (Orocecal Transit Time – OCTT) e tempo de trânsito intestinal (Small Intestinal Transit Time – SITT), considerando as variações impostas pelos estados prandiais (jejum/alimentado), bem como os efeitos da viscosidade e da pressão intragástrica.

Os ensaios in vitro revelaram que tanto a viscosidade do meio quanto a pressão intragástrica impactam diretamente o desempenho do sistema flutuante. A elevação da viscosidade, simulando o estado alimentado (até 320 mPa·s), e o aumento da pressão intragástrica (até 1060 mmHg) resultaram em aumentos significativos no FLT, que variou de 4,46 ± 0,88 minutos em condições basais para até 38 ± 2,07 minutos nas condições de maior pressão e viscosidade. Esse atraso no início da flutuação está relacionado à maior resistência oferecida pelo meio para a difusão de fluidos para o interior da matriz, além do efeito mecânico da compressão causada pela pressão elevada. Observou-se também um aumento na área magnética do comprimido durante os testes, refletindo o processo de intumescimento da matriz e a subsequente redução da densidade até atingir a flutuabilidade. Nos estudos in vivo, conduzidos com voluntários saudáveis, os dados confirmaram os achados in vitro e forneceram uma visão mais abrangente do comportamento da formulação. No estado alimentado, os

parâmetros FLT, GRT, OCTT e SITT apresentaram aumentos expressivos em relação ao estado de jejum. O FLT variou de 73,1 ± 16,9 minutos (jejum) para 107,5 ± 29,8 minutos (alimentado), enquanto o GRT passou de 139,4 ± 25,3 minutos para 190,2 ± 47,7 minutos, demonstrando uma retenção significativamente prolongada no estômago quando associado à presença de alimento. De forma similar, o OCTT aumentou de 241,9 ± 18,7 minutos (jejum) para 300 ± 46,4 minutos (alimentado), e o SITT, calculado pela diferença entre OCTT e GRT, apresentou elevação de 102,5 ± 14,8 minutos no estado de jejum para 109,8 ± 18,7 minutos no estado alimentado, indicando que o trânsito pelo intestino delgado sofreu leve aumento, mas de menor magnitude em relação às variações observadas na fase gástrica.

A análise farmacocinética, realizada de forma integrada à monitorização biomagnética (farmacomagnetografia), revelou que os parâmetros cinéticos foram diretamente impactados pela variação no tempo de retenção gástrica. No estado de jejum, o tempo para atingir a concentração plasmática máxima (Tmax) foi de 2,3 ± 0,4 horas, enquanto no estado alimentado aumentou para 3,7 ± 0,5 horas, refletindo o prolongamento da retenção gástrica e o atraso na liberação do fármaco. A concentração plasmática máxima (Cmax) também sofreu alteração, reduzindo-se de 4,8 ± 0,7 µg/mL (jejum) para 3,9 ± 0,5 µg/mL (alimentado), evidenciando uma liberação mais gradual da substância. Por outro lado, a área sob a curva ($AUC_{0-\infty}$) aumentou de 27,5 ± 3,4 µg·h/mL (jejum) para 31,8 ± 4,1 µg·h/mL (alimentado), demonstrando que a retenção gástrica prolongada favoreceu um aumento na biodisponibilidade total do fármaco. De forma integrada, os resultados demonstram que o sucesso dos sistemas gastrorretentivos está diretamente condicionado à interação entre os aspectos farmacotécnicos da formulação como a composição polimérica, a eficiência do agente gerador de gás e a incorporação do marcador magnético e os fatores fisiológicos como viscosidade do conteúdo intragástrico, pressão interna do estômago e padrões de motilidade regulados pelo complexo motor migratório (CMM). A técnica BAC demostrou-se uma ferramenta robusta, não invasiva, precisa e de baixo custo, capaz de monitorar em tempo real o posicionamento e o comportamento da forma farmacêutica no trato gastrointestinal, além de possibilitar a correlação direta entre tempos de trânsito e os parâmetros farmacocinéticos, consolidando a farmacomagnetografia como uma abordagem metodológica inovadora no desenvolvimento de formas farmacêuticas de liberação modificada. Portanto, este estudo fornece uma contribuição significativa para o avanço das tecnologias de liberação controlada, apresentando não apenas um sistema farmacêutico flutuante magnético eficaz, mas também uma metodologia analítica que permite avaliar de forma abrangente a

interação entre formulação e fisiologia gastrointestinal, com aplicações diretas tanto em pesquisa quanto em desenvolvimento industrial e clínico.

Palavras-chave: Sistemas gastrorretentivos; Farmacomagnetografia; Metronidazol; Biosusceptometria de Corrente Alternada; Estado prandial; Biodisponibilidade.

ABSTRACT

The present study aimed to develop, characterize, and evaluate a magnetic floating tablet capable of prolonging gastric retention time (GRT), optimizing the absorption and bioavailability of drugs whose therapeutic window is located in the proximal portion of the gastrointestinal tract. The proposal was based on the application of the Alternating Current Biosusceptometry (ACB) technique as a non-invasive tool for real-time monitoring of the gastrointestinal behavior of the pharmaceutical form, allowing the correlation of pharmaceutical parameters (in vitro), transit parameters, and pharmacokinetic profiles (pharmacomagnetography/in vivo). The formulation developed consisted of a polymeric matrix containing hydroxypropyl methylcellulose (HPMC), a gas-generating effervescent agent (sodium bicarbonate), and manganese ferrite as the magnetic marker. In vitro studies were conducted to evaluate the influence of simulated physiological variables (viscosity and intragastric pressure) on the performance of the pharmaceutical form. For this purpose, experiments were conducted in media with varying viscosities (1, 50, 120, and 320 mPa·s) and under different intragastric pressures (760, 910, and 1060 mmHg), representing both fasting and fed stomach conditions. Parameters such as Floating Lag Time (FLT), Gastric Retention Time (GRT), Orocecal Transit Time (OCTT), and Small Intestinal Transit Time (SITT) were evaluated, considering the variations imposed by prandial states (fasting/fed), as well as the effects of viscosity and intragastric pressure. The in vitro assays revealed that both the medium's viscosity and intragastric pressure directly impact the performance of the floating system. The increase in viscosity, simulating the fed state (up to 320 mPa·s), and the increase in intragastric pressure (up to 1060 mmHg) resulted in significant increases in FLT, which ranged from 4.46 ± 0.88 minutes under baseline conditions to up to 38 ± 2.07 minutes under the highest pressure and viscosity conditions. This delay in the onset of flotation is related to the greater resistance of the medium to fluid diffusion into the matrix, as well as the mechanical compression effect caused by elevated pressure. An increase in the magnetic area of the tablet was also observed during the tests, reflecting the matrix swelling process and the subsequent reduction in density until flotation was achieved.

In vivo studies conducted with healthy volunteers confirmed the in vitro findings and provided a more comprehensive view of the formulation's behavior. In the fed state, the FLT, GRT, OCTT, and SITT parameters showed significant increases compared to the fasting state. FLT ranged from 73.1 ± 16.9 minutes (fasting) to 107.5 ± 29.8 minutes (fed), while GRT increased from 139.4 ± 25.3 minutes to 190.2 ± 47.7 minutes, demonstrating significantly

prolonged retention in the stomach when associated with food intake. Similarly, OCTT increased from 241.9 ± 18.7 minutes (fasting) to 300 ± 46.4 minutes (fed), and SITT, calculated as the difference between OCTT and GRT, increased from 102.5 ± 14.8 minutes in the fasting state to 109.8 ± 18.7 minutes in the fed state, indicating that the transit through the small intestine showed a slight increase but of lesser magnitude compared to the variations observed in the gastric phase.

Pharmacokinetic analysis, performed in an integrated manner with biomagnetic monitoring (pharmacomagnetography), revealed that kinetic parameters were directly impacted by changes in gastric retention time. In the fasting state, the time to reach maximum plasma concentration (Tmax) was 2.3 ± 0.4 hours, while in the fed state, it increased to 3.7 ± 0.5 hours, reflecting the prolonged gastric retention and the delayed drug release. The maximum plasma concentration (Cmax) also changed, decreasing from 4.8 ± 0.7 µg/mL (fasting) to 3.9 ± 0.5 µg/mL (fed), indicating a more gradual release of the substance. On the other hand, the area under the curve (AUC0-∞) increased from 27.5 ± 3.4 µg·h/mL (fasting) to 31.8 ± 4.1 µg·h/mL (fed), demonstrating that prolonged gastric retention favored an increase in the total bioavailability of the drug. Taken together, the results demonstrate that the success of gastroretentive systems is directly conditioned by the interaction between the pharmaceutical formulation's technical aspects such as the polymer composition, the efficiency of the gas-generating agent, and the incorporation of the magnetic marker and physiological factors such as the viscosity of the intragastric content, internal stomach pressure, and motility patterns regulated by the migrating motor complex (MMC). The ACB technique proved to be a robust, non-invasive, precise, and low-cost tool capable of real-time monitoring of the positioning and behavior of the pharmaceutical form within the gastrointestinal tract. Additionally, it allowed a direct correlation between transit times and pharmacokinetic parameters, consolidating pharmacomagnetography as an innovative methodological approach in the development of modified-release pharmaceutical forms. Therefore, this study provides a significant contribution to the advancement of controlled-release technologies, presenting not only an effective magnetic floating pharmaceutical system but also an analytical methodology that allows a comprehensive evaluation of the interaction between formulation and gastrointestinal physiology, with direct applications in research, industrial development, and clinical practice.

Keywords: Gastroretentive systems; Pharmacomagnetography; Metronidazole; Alternating Current Biosusceptometry; Prandial state; Bioavailability.

INTRODUÇÃO GERAL

Nas últimas décadas, a humanidade tem enfrentado diferentes tipos de desafios na saúde humana. Alcançar a máxima eficácia terapêutica com o menor risco de efeitos adversos é um dos principais objetivos no tratamento de uma doença. Nesse cenário, a indústria farmacêutica tem direcionado seus esforços para o desenvolvimento de formulações inovadoras que proporcionem terapias mais eficazes e seguras (1, 2).

Durante a elaboração de uma formulação ou de um sistema de liberação de fármacos, é essencial considerar fatores como a forma farmacêutica, os excipientes utilizados e as propriedades físico-químicas da substância ativa, pois esses elementos influenciam diretamente na performance terapêutica do medicamento. Além disso, a escolha da via de administração é outro fator importante, uma vez que o fármaco deve ter biodisponibilidade adequada para o efeito desejado. Dentre as vias disponíveis, a via oral tem se destacado como a mais utilizada para administração de fármacos, por ser uma via que apresenta baixo custo, simplicidade na administração e flexibilidade na formulação, resultando em elevada aceitação e adesão por parte dos pacientes (3, 4).

Sendo assim, é um alvo de grande interesse da indústria farmacêutica, que se empenha fortemente no desenvolvimento de formulações que objetivam otimizar a absorção de fármacos no trato gastrintestinal (TGI) (5, 6). O objetivo principal de qualquer sistema de liberação de fármacos é garantir que a substância ativa atinja o local desejado no organismo de forma rápida e com liberação prolongada. Estima-se que os medicamentos administrados por via oral correspondam a mais da metade das estratégias de liberação de fármacos disponíveis no mercado (7).

Entretanto, a eficiência da administração oral pode ser afetada por diversos fatores, como os biofarmacêuticos e principalmente fisiológicos, como o tempo de trânsito gastrointestinal, o local de absorção do medicamento e o esvaziamento gástrico. Muitas formas orais enfrentam limitações fisiológicas significativas, especialmente relacionadas à variabilidade no esvaziamento gástrico, o que pode gerar perfis de absorção irregulares, liberação inadequada do princípio ativo e menor tempo de retenção do medicamento no estômago. Como resultado, certos fármacos podem ter uma janela de absorção insuficiente e permanecerem não absorvidos, especialmente na parte superior do intestino delgado. Além do tempo de esvaziamento gástrico varia consideravelmente entre diferentes indivíduos e até mesmo no mesmo indivíduo em condições distintas (8, 9). Diante desse cenário, o

desenvolvimento de formas farmacêuticas para liberação modificada (FFLM) de fármacos têm sido alvo de inúmeras investigações. Esses sistemas liberam o fármaco de forma gradual, fornecendo uma vantagem sobre as formas farmacêuticas convencionais, otimizando as propriedades biofarmacêuticas, farmacocinéticas e farmacodinâmicas dos fármacos, de forma a reduzir a frequência de administração da forma farmacêutica, sendo que uma dose ao dia seja o suficiente para que se mantenha a máxima atividade terapêutica do fármaco por meio da possibilidade do controle da concentração plasmática, garantindo que no menor tempo possível, com a menor quantidade de fármaco, seja possível garantir uma melhor adesão do paciente ao tratamento.

Os sistemas gastrorretentivos (GRDDS – Gastro Retentive Drug Delivery Systems) constituem uma classe de sistemas de liberação controlada cujo principal objetivo é a extensão do tempo de retenção gástrica (TRG), permitindo que o fármaco permaneça por mais tempo no estômago e favorecendo sua absorção em regiões específicas do trato gastrointestinal superior. Esta abordagem é particularmente vantajosa para princípios ativos que apresentam janela de absorção limitada, instabilidade em ambientes colônicos ou que atuam localmente no estômago (10-12).

Nos últimos anos, diversas estratégias têm sido desenvolvidas com o objetivo de prolongar a TRG das formas farmacêuticas orais, consolidando o GRDDS como uma alternativa promissora dentro da área de sistemas de liberação modificada. Dentre essas estratégias, destacam-se: mecanismos de flutuação (sistemas que são capazes de flutuar no conteúdo gástrico), de bioadesão (sistemas que aderem à parede do estômago), expansíveis (sistemas nos quais o comprimido aumenta de tamanho e, assim, dificulta sua passagem pelo piloro) e magnéticos (sistemas que utilizam campos magnéticos externos para manter a forma farmacêutica na região gástrica), que buscam contornar as barreiras fisiológicas impostas pela motilidade gástrica e pela variabilidade interindividual no esvaziamento gástrico (13-15).

Os sistemas flutuantes representam um dos sistemas de liberação prolongada e vêm sendo considerados alternativas promissoras para fármacos que apresentam esvaziamento gástrico imprevisível e curta permanência no estômago. Estes sistemas apresentam densidades inferiores à do fluido gástrico (aproximadamente 1.004 g/cm^3) e flutuam no estômago por um período de tempo prolongado, sem afetar a taxa de esvaziamento gástrico. Enquanto o sistema está flutuando no conteúdo gástrico, o fármaco é liberado gradualmente. Devido a sua permanência na superfície do fluido intragástrico, os mecanismos de propulsão do órgão não conseguem aproximá-lo do piloro, promovendo maior tempo de retenção no estômago. São

especialmente vantajosos em casos nos quais a biodisponibilidade e a solubilidade do princípio ativo são reduzidas. A eficácia terapêutica de um medicamento depende da sua concentração no sítio de ação, e, nesse contexto, os sistemas flutuantes contribuem significativamente ao prolongar o tempo de residência gástrica (TRG), favorecendo uma liberação controlada e contínua do fármaco.

Os sistemas flutuantes de liberação controlada podem ser classificados em dois grandes grupos: efervescentes e não efervescentes. Os sistemas efervescentes utilizam matrizes poliméricas de características hidrofóbicas, expansíveis ou compostas por polissacarídeos, nas quais são incorporados compostos geradores de gás, como o bicarbonato de sódio. Quando em contato com o ambiente ácido do estômago, ocorre a liberação de dióxido de carbono (CO_2), fenômeno essencial para proporcionar a flutuação da forma farmacêutica. Em contraste, os sistemas não efervescentes são baseados em polímeros hidrofílicos que, ao absorverem o conteúdo gástrico, se expandem e diminuem sua densidade relativa, permitindo que a forma farmacêutica permaneça suspensa no estômago (16-18).

Uma limitação importante é a necessidade de volume suficiente de fluido gástrico para garantir a flutuabilidade da forma farmacêutica. Para contornar esse desafio, outra forma tipo mucoadesivas são estudas e sao baseadas em polímeros com propriedades bioadesivas, como carbopol, HPMC, dextrana, tragacanto, quitosana, alginato de sódio, polietilenoglicol, ácido poliacrílico e ácido poliláctico, são incorporados à formulação. Esses materiais têm a capacidade de aderir à mucosa gástrica, o que contribui para prolongar o tempo de residência no estômago, melhorar a absorção de fármacos com janela de absorção na porção superior do trato gastrointestinal e reduzir a frequência de administração (19, 20).

Diversas subclasses são descritas dentro dessa categoria, incluindo esferas de alginato, sistemas hidrodinamicamente balanceados (Hydrodynamically Balanced Systems – HBS), microesferas ocas e sistemas compartimentados microporosos, todos projetados para prolongar a permanência do fármaco no estômago e otimizar sua biodisponibilidade local ou sistêmica (21, 22).Os excipientes mais comuns em sistemas não efervescentes incluem hidrocoloides gelificantes, celulose altamente expansível, polissacarídeos e polímeros formadores de matrizes como poliacrilato, polimetacrilato, policarbonato e poliestireno. Pesquisadores, como Prajapati et al. (23), sugerem que, ao entrar em contato com um meio aquoso, o hidrocolóide passa por um processo de hidratação, formando inicialmente um gel em sua superfície. Esse gel hidrocolóide cria um estrato gelificado durante a hidratação, no qual o fármaco se dissolve

internamente e se difunde para o exterior, sendo a difusão controlada por essa camada de gel hidrocoloide (24-27).

Por outro lado, a extensão do tempo de retenção gástrica (TRG) das formas farmacêuticas no estômago representa uma estratégia promissora com importantes implicações terapêuticas e biofarmacêuticas. Entre os principais benefícios, destacam-se a potencialização da ação local de fármacos destinados ao TGI, a diminuição das variações nos níveis plasmáticos prevenindo tanto concentrações subterapêuticas quanto níveis tóxicos, e a melhora na adesão do paciente ao tratamento farmacológico. Adicionalmente, o prolongamento do TRG possibilita a redução na frequência das administrações e favorece a biodisponibilidade de fármacos cuja absorção ocorre predominantemente no estômago ou na porção proximal do intestino delgado ou ainda no caso de fármacos que sejam degradados ou pouco solúveis em pH alcalino ou que apresentem janela estreita de absorção (28-31).

Diversos fármacos se beneficiam dessa tecnologia, entre eles o metronidazol, utilizado no tratamento de infecções gastrintestinais; a ranitidina e o omeprazol, indicados em distúrbios gástricos como úlceras e refluxo gastroesofágico; e o levodopa, usado no manejo da doença de Parkinson, cuja absorção é favorecida em regiões proximais do trato gastrointestinal (32, 33). Outros exemplos incluem a ciprofloxacina, furosemida, verapamil e gabapentina, cujas propriedades farmacocinéticas tornam vantajosa a formulação em sistemas gastrorretentivos (34, 35).

É importante destacar que os sistemas que prolongam o tempo de retenção gástrica (TRG) são amplamente empregados no tratamento de infecções por Helicobacter-pylori, que afeta principalmente o estômago. Essa bactéria está diretamente relacionada a condições patológicas, como câncer gástrico, e outras doenças graves do trato gastrointestinal (TGI), incluindo gastrites, úlceras pépticas e duodenais, adenocarcinoma gástrico e neoplasia colorretal (36-38). Isso ressalta a importância de estratégias que visem aumentar o TRG. O trato gastrointestinal impõe barreiras que tecnologias convencionais frequentemente não conseguem transpor. Assim, o grande desafio no desenvolvimento de sistemas de liberação controlada não se limita à manutenção da liberação do medicamento, mas também envolve o prolongamento da permanência da formulação no estômago ou na porção proximal do intestino delgado até que a totalidade da dose seja administrada na velocidade terapêutica desejada (39-42).

Apesar de ser amplamente utilizada, a administração oral de medicamentos pode enfrentar obstáculos físicos devido à complexidade do trato gastrointestinal (TGI). Diversos fatores que variam ao longo do TGI interferem diretamente na absorção dos princípios ativos, especialmente no que diz respeito à interação da formulação com os parâmetros fisiológicos,

como motilidade, viscosidade do conteúdo gástrico e pressão intragástrica (43, 44). As avaliações *in vivo* são essenciais para compreender o desempenho dos sistemas gastrorretentivos, no entanto, antes da realização dos estudos *in vivo*, se torna fundamental conduzir testes *in vitro* que simulem diferentes condições fisiológicas associadas aos estados prandiais (jejum e alimentado). Desta forma, no Capitulo 1 é apresentado o estudo para avaliar diferentes parâmetros como a viscosidade e a pressão intragástrica, os quais são diretamente impactados pela presença ou ausência de alimento no estômago. Por meio desses ensaios, foi possível prever com maior precisão o comportamento do comprimido magnético flutuante, avaliando-se, principalmente, o tempo de início de flutuação (Floating Lag Time - FLT), que se mostrou diretamente influenciado pela resistência mecânica do meio (pressão) e pela dificuldade de difusão do meio externo para o interior da matriz (viscosidade). Essas avaliações forneceram uma base sólida para a formulação, permitindo desenvolver sistemas mais robustos e capazes de se adaptar às condições fisiológicas reais, otimizando, assim, seu desempenho no trato gastrointestinal.

A eficácia dos sistemas gastrorretentivos em condições *in vivo* é fortemente influenciada não apenas por propriedades biofarmacêuticas da formulação, mas, sobretudo, por fatores fisiológicos do trato gastrointestinal (TGI). Entre estes, a motilidade gástrica constitui uma variável crítica, principalmente em função do estado alimentar do paciente jejum ou alimentado sendo regulada por um mecanismo fisiológico conhecido como Complexo Motor Migratório (CMM). O CMM é um padrão de atividade peristáltica cíclica, observado durante o estado de jejum, que se propaga do estômago até o íleo terminal. Sua função primordial é promover a varredura mecânica do trato digestivo, eliminando resíduos sólidos não digeridos e secreções. Este ciclo é dividido em quatro fases sucessivas, com duração total média de 90 a 120 minutos, e apresenta variações interindividuais significativas.

A fase I, também denominada fase de quiescência, é caracterizada por um período de repouso motor com ausência quase total de contrações gástricas, durando entre 40 e 60 minutos. Em seguida, ocorre a fase II, marcada pelo início de contrações esporádicas e de baixa amplitude, que aumentam progressivamente em frequência e intensidade, com duração aproximada de 20 a 40 minutos. A fase III, considerada a fase de atividade máxima, corresponde ao momento de maior importância para o esvaziamento gástrico de formas sólidas, caracterizada pelas denominadas ondas de limpeza (housekeeping waves) (34, 45-47). Nela, há contrações peristálticas intensas, rítmicas e de alta amplitude, propagando-se em ondas que percorrem o estômago e o intestino delgado, com duração média de 4 a 6 minutos. Finalmente, a fase IV representa uma curta transição que marca o fim da atividade motora intensa e o retorno

ao estado de repouso da fase I. Durante o estado pós-prandial, o CMM é suprimido em função da presença de alimento, sendo substituído por um padrão de contrações mais contínuas e menos intensas, que promovem o esvaziamento gradual do conteúdo gástrico. Esse ambiente é favorável à retenção de sistemas flutuantes ou de dispositivos expansíveis, uma vez que reduz significativamente o risco de expulsão imediata do estômago. No entanto, após a digestão, o CMM é reativado, e o tempo para seu reinício pode variar consideravelmente entre os indivíduos, podendo chegar até 180 minutos. Essa variabilidade representa um importante desafio para o desenvolvimento de sistemas gastrorretentivos eficazes e previsíveis. Dessa forma, o conhecimento aprofundado da fisiologia gástrica, especialmente dos padrões de motilidade regulados pelo CMM, é essencial para o desenho racional de sistemas de liberação controlada. A interação entre essas fases e o tempo de esvaziamento gástrico afeta diretamente a biodisponibilidade, o perfil de liberação e a eficácia terapêutica das formas farmacêuticas desenvolvidas para permanecer no estômago por períodos prolongados. Portanto, para o desenvolvimento eficaz de novos produtos ou esquemas terapêuticos, é essencial compreender a fisiologia normal do trato gastrointestinal e suas alterações (48-51).

Para o desenvolvimento de novos produtos farmacêuticos e de estratégias terapêuticas mais eficazes, é fundamental compreender tanto a fisiologia normal do trato gastrointestinal (TGI) quanto suas possíveis alterações. Isso porque variáveis fisiológicas, associadas às características físico-químicas e farmacotécnicas dos medicamentos, exercem influência direta sobre a absorção e biodisponibilidade dos fármacos administrados por via oral. Diante desse cenário, torna-se indispensável a adoção de métodos de análise que permitam caracterizar o comportamento de sistemas gastrorretentivos flutuantes, tanto *in vitro* quanto *in vivo*, possibilitando, assim, estabelecer uma correlação efetiva entre os dados obtidos em ambos os ambientes (28, 52-55).

Entre os métodos tradicionalmente empregados para esse fim, destaca-se a cintilografia, considerada um dos padrões-ouro na avaliação do trânsito gastrointestinal em estudos clínicos. Nessa técnica, a forma farmacêutica é marcada com radionuclídeos emissores de radiação gama e, em seguida, monitorada por meio de uma gama-câmara. Entretanto, além dos riscos associados à exposição à radiação ionizante, a cintilografia apresenta limitações importantes, como o elevado custo dos radiofármacos adequados para uso em farmacotécnica, a necessidade de infraestrutura especializada com equipamentos/ambientes blindados e a baixa resolução anatômica, que impede uma localização precisa da forma farmacêutica no TGI (56-58).

Como alternativa promissora e não invasiva, destacam-se os métodos baseados em biomagnetismo, os quais têm sido amplamente aplicados tanto na pesquisa farmacotécnica quanto em estudos fisiológicos do TGI. Essas metodologias permitem avaliar parâmetros como motilidade gastrointestinal, esvaziamento gástrico e trânsito intestinal, além de apresentarem aplicações clínicas, inclusive na medicina nuclear. O princípio dessas técnicas reside na detecção de campos magnéticos sejam eles oriundos da atividade elétrica biológica ou gerados por materiais magnéticos introduzidos no organismo e estimulados por campos externos. Dentre os materiais mais utilizados destacam-se as ferritas e a magnetita, que são biologicamente inertes, não sendo absorvidos pelo organismo e sendo eliminados de forma segura por vias fisiológicas, como urina ou fezes. As principais tecnologias que exploram esse princípio incluem os dispositivos supercondutores de interferência quântica (SQUID), sensores anisotrópicos magnetorresistivos (AMR), a ressonância magnética (MRI) e a biosusceptometria de corrente alternada (BAC) (32, 33, 59, 60).

A BAC, em especial, tem se destacado como uma técnica inovadora para o monitoramento do TGI, por ser totalmente não invasiva, isenta de radiação ionizante, não demandar ambientes blindados e apresentar custos operacionais consideravelmente inferiores quando comparada às técnicas convencionais e poder avaliar tanto a motilidade gastrintesnal (atividade de contração gástrica) e trânsitos gastrintestinal. O princípio operacional da BAC fundamenta-se na utilização de um sistema gradiométrico, que funciona como um transformador duplo de fluxo magnético, composto por dois pares de bobinas um par de excitação e outro de detecção. O par mais distante da amostra magnética atua como referência, enquanto o par mais próximo é responsável pela detecção do sinal. Quando um material ferromagnético se aproxima das bobinas de detecção, ocorre um desbalanceamento no fluxo magnético do sistema, resultando no aumento do sinal elétrico captado. Esse sinal é posteriormente amplificado por um dispositivo sensível à fase (Lock-in), convertido de analógico para digital por meio de uma placa A/D e, então, processado e registrado em tempo real por um computador. Na prática, os dados obtidos são organizados em matrizes temporais, que podem ser processadas para gerar imagens sequenciais do comportamento dos materiais magnéticos no interior do trato gastrointestinal, permitindo acompanhar seu deslocamento e dinâmica ao longo do tempo.

Diante desse contexto, este trabalho propõe a aplicação da técnica de Biosusceptometria de Corrente Alternada para o monitoramento de sistemas flutuantes magnéticos no estômago de voluntários saudáveis, avaliando seu comportamento sob diferentes condições alimentares (jejum e alimentado). Embora a BAC já tenha sido utilizada na avaliação de sistemas

monolíticos e multiparticulados, este estudo busca inovar ao aplicá-la no acompanhamento de sistemas gastrorretentivos. Além disso, pretende-se integrar os dados obtidos por meio do monitoramento biomagnético aos perfis farmacocinéticos dos fármacos, permitindo uma análise aprofundada da interação entre a fisiologia gastrointestinal e os mecanismos de liberação dos medicamentos, correlacionando tempos de trânsito com parâmetros farmacocinéticos — conceito conhecido como farmacomagnetografia.

Este estudo está dividido em dois trabalhos, nos quais no Capitulo 1 abordamos a confecção e testes de viabilidade da forma flutuante magnética e viabilidade de aplicação, e no Capitulo 2 avalia-se a magnetofamacocinetica propriamente dito, correlacionando dados magnéticos e cinéticos frente a diferente estado prandial.

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Capitulo 1

pharmaceutics

Article

In Vitro and In Vivo Evaluation of Magnetic Floating Dosage Form by Alternating Current Biosusceptometry

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Abstract: Floating controlled systems seek to extend the gastric retention time (GRT) of solid pharmaceutical forms by sustaining buoyancy in the stomach without affecting gastric emptying rates. This investigation aimed to evaluate a magnetic floating drug delivery system (MFDDS) under diverse physiological conditions (pressure and viscosity) using an Alternating Current Biosusceptometry (ACB) system by conducting assessments *in vitro* and *in vivo*. For *in vitro* experiments, MFDDSs were placed under different pressures (760, 910, and 1060 mmHg) and viscosities (1, 50, 120, and 320 mPa·s) for evaluation of floating lag time (FLT). For *in vivo* experiments, eight healthy volunteers participated in two phases (fasting and fed) for gastric parameters (GRT, FLT, and OCTT—orocaecal transit time) assessment, employing the ACB system. The results indicated that pressure, viscosity, and FLT were directly proportional in the *in vitro* assay; in addition, increases in the OCTT (fasting = 241.9 ± 18.7; fed = 300 ± 46.4), GRT (fasting = 139.4 ± 25.3; fed = 190.2 ± 47.7), and FLT (fasting = 73.1 ± 16.9; fed = 107.5 ± 29.8) were detected *in vivo*. Our study emphasizes that the ACB system is a valuable technique, and it is capable of tracking and imaging MFDDS in *in vitro* and *in vivo* experiments.

Keywords: ACB system; magnetic floating drug delivery systems; floating lag time (FLT); viscosity; intragastric pressure

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1. Introduction

The oral route is essential in therapy as it is the most preferred and convenient route for drug delivery systems. The development of pharmaceutical forms for controlled drug release has been the target of numerous researchers over the years. Gastroretentive drug delivery systems (GRDDS) are a type of controlled drug release system [1–3]. The GRDDS are specially designed to increase the residence time of the dosage form in the stomach (gastric retention time, GRT). Such systems offer a substantial advantage over traditional pharmaceutical forms by ensuring a gradual release of the drug. A prolonged stay of dosage forms within the stomach, known as gastroretention, offers several therapeutic and biopharmaceutical advantages [4–6]. These advantages encompass enhanced drug effectiveness in the stomach, reduced variations in drug concentration plasma, increased patient adherence due to reduced dosing frequency, and improved bioavailability for specific medications that require absorption in the upper small intestine [6–9]. These systems are particularly beneficial for a range of medicines, such as those intended to act in the stomach itself, drugs with limited absorption capabilities in the upper stomach or small intestine, and substances with poor solubility in alkaline conditions (e.g., diazepam) [10,11]. Several types of GRDDS have been developed to increase the gastric retention time of pharmaceutical forms in the stomach, such as floating, bioadhesive, and expanding [12–15].

A floating drug delivery system represents a significant category of gastroretentive drug de- livery mechanisms. These systems possess densities lower than gastric fluid (approximately 1.004 g/cm^3), allowing them to float within the stomach for an extended duration without influencing gastric emptying [16,17]. They release the drug gradually while floating in the gastric contents. Their buoyancy ensures they remain distanced from the pylorus, extending their stomach stay. Consequently, these systems are primarily eliminated during the later stages of gastric emptying, resulting in an increased residence time in the stomach and enhanced regulation of fluctuations in drug plasma concentration [18–21].

However, the efficiency of gastroretentive systems in an *in vivo* situation is influenced by biopharmaceutical parameters and mainly by parameters related to the GIT. The biggest obstacle to gastroretentive systems is gastric motility, especially in the prandial state (fasting/fed) [22–26]. This state has different phases of mechanical contraction activity, with phase III being characterized by the so-called housekeeping waves [27,28]. These phases can influence the time the solid pharmaceutical form remains in the stomach, and the prandial state can affect the viscosity, density of the food bolus, and pH [29–33].

In addition to the physiological changes that occur in the stomach under conditions of prandial state (fasting/fed), little attention is paid to intragastric pressures and viscosity of the medium that act on gastroretentive systems [34–39]. Recent studies show that high intragastric pressures have increased the release rate of gastroretentive pharmaceutical forms [36,40,41]. This occurs primarily in the case of polymer matrix tablets and hydrogels, which are highly sensitive to these pressures, and their release rates are determined through the erosion caused by these pressures on the tablets, mainly in a prandial state (fed) [42,43]. Due to these pressures, the release rate is increased significantly, which explains irregular drug concentration profiles in plasma [27,39,44,45]. Another factor that can affect these systems is the varying viscosity of the environments in which they are placed, such as the gastric contents in the fasting and fed states [34,40,46–48]. The viscosity of the gastric environment can influence the floating time (or even the floating process) and, conse- quently, impair the drug release rate and the retention of the pharmaceutical form in the stomach [49]. Therefore, simultaneous food intake can modify the systemic availability of many medications, potentially affecting their therapeutic effectiveness, in addition to the fact that the prandial state interferes with motility.

Given that physiological factors associated with the human gastrointestinal tract substantially impact the absorption and bioavailability of orally administered drugs and considering the high costs and complexity of interpreting data from clinical trials in humans, it has become sensible to employ analytical techniques to evaluate floating systems.

Therefore, non-invasive technologies that can monitor a magnetic floating drug de- livery system (MFDDS) *in vitro* and across GIT segments under different conditions are needed. Biomagnetic techniques to non-invasively monitor MFDDSs currently constitute a viable alternative for pharmaceutical research carried out *in vitro* and studies related to the physiology of the gastrointestinal tract (GIT) in humans and animals [50–53]. Alter- nating Current Biosusceptometry (ACB) is a biomagnetic technique used as an alternative approach in pharmaceutical research to evaluate the *in vitro* performance of solid dosage forms [13]. Furthermore, it is used to monitor the transit of these forms through the different segments of the gastrointestinal tract (GIT) [50,54,55]. This methodology uses ferrite powder as a tracer, an inert material, presenting stability in different pH conditions throughout the GIT, whether in acidic or basic environments [56,57]. The ACB method is based on the use of induction coils to record magnetic flux variations obtained from a magnetically susceptible material in response to the application of an alternating magnetic field [50,54]. Furthermore, it serves as a complementary tool for quality control of MDFFSs.

Previous studies have demonstrated the efficiency of the ACB system when applied in pharmaceutical research, correlatively evaluating gastric transit (GIT) and the phar- macokinetics of magnetic dosage forms (pharmacomagnetography). This methodology involves incorporating magnetic elements into pharmaceutical formulations, such as tablets or capsules, allowing real-time transit and disintegration monitoring using external mag-

netic sensors with imaging techniques. Thus, pharmacomagnetography is valuable for simultaneously studying drug distribution, gastrointestinal motility, and drug absorption kinetics [58–60].

Thus, the objective of this study was to evaluate an MFDDS *in vitro* and *in vivo* under different physiological conditions (fasting and fed states) using the ACB system.

2. Materials and Methods

2.1 Materials

The following materials were used to manufacture the floating magnetic tablets used in these studies: Ferrite powder ($MnFe_2O_4$; diameter of $90 < \phi < 125$ μm)—Thornton (Vinhedo, Brazil) was used as the magnetic marker; HPMC (Methocel E4M) was donated from Colorcon (Cotia, Brazil); lactose, PVP K30, magnesium stearate, and sodium starch glycolate were obtained from Henrifarma (São Paulo, Brazil); hydroxyethyl cellulose (HEC)—Colorcon (Indaiatuba, Brazil); and sodium bicarbonate—Audaz (São Paulo, Brazil). All other reagents and solvents were of analytical grade.

2.2 Floating Magnetic Tablets

The tablets were prepared using manganese ferrite powder (430 mg, 35.83%), magne- sium stearate (18 mg, 1.5%), hydroxypropylmethylcellulose (HPMC E4M—430 mg, 35.83%), lactose (152 mg, 12.6%), polyvinylpyrrolidone (PVP K30) (10 mg, 0.83%), and sodium bicar- bonate (160 mg, 13.3%). All the excipients were mixed and manually manufactured using a single punch machine (Erweka, EKOTM, Langen (Hessen), Germany) with a flat face and a 12 mm diameter at a pressure of 30 kN. Each tablet contained 1.2 g. In the present study, magnetic floating drug delivery system (MFDDS) tablet formulations were tested according to the outline in the US Pharmacopeia. Therefore, the average weight, hardness, and friability were assessed for all tablet formulations.

In the study, solutions were prepared using a specific method to simulate gastric fluid and create solutions with varying viscosities. The following steps were followed: A simulated gastric fluid was designed according to USP 23 with (SGF) and without pepsin (SGF). The solution consisted of 900 mL of distilled water and 1.6 mL of 0.1 N HCl and was checked on a calibrated pH meter (Hanna pH 210, Smithfield, VA, USA) until it reached pH 1.2. The solution was maintained at 37 ± 0.5 °C for 30 min in a water bath to replicate body temperature.

To create solutions with different viscosities, a beaker containing 330 mL of distilled water was preheated in a water bath at 80 °C. After performing the preliminary screen- ing study, hydroxypropylmethylcellulose (Methocel K4M, Colorcon Co., Dartford, UK) was selected as a chemically inert, water-soluble, relatively readily dispersible non-ionic polymer aimed to mimic the effect of increased viscosity. Once the desired temperature (80 °C) was reached, varying amounts of the polymer HEC (2, 4, and 6 g) were weighed and added to the solution. The solution was stirred at 75 rpm using a magnetic stirrer for 30 min until it cooled to room temperature. Subsequently, 670 mL of distilled water was added, totaling 1 L of solution. This solution was continuously agitated for 12 h (overnight). The temperature of 80 °C was maintained to ensure complete dissolution of the polymer particles. After 12 h, the pH of the solutions was measured.

These procedures were carried out to create solutions with different concentrations of HEC polymer and varying viscosities while replicating gastric and body temperature conditions. These solutions were employed in the study to evaluate various parameters of interest.

2.3 Rheological Measurements

Rheological measurements were performed using the Brookfield RV viscometer (Wa- ters Technologies—São Paulo, Brazil). The spindle used was the SC4-14, which had a 40 mm diameter, an angle of 1°, and a spindle-to-sample gap that varied from 0.1 to 80 Pa·s. The initial rotational speed of the viscometer was set at 1 rpm and was gradually increased until

reaching a final speed of 170 rpm. Data were recorded at 20 different rotational speeds, and each data point had a recording time of two minutes. The shear rate ranged from 0.05 s^{-1} to 80 s^{-1}, covering a wide range of flow conditions. Media samples were preheated at 37 °C. All measurements were performed in triplicate.

2.4 Floating Assessment and Magnetic Method by ACB

In vitro measurements and exploratory procedures were conducted to assess the floatability of the proposed formulation for subsequent project phases. Three random tablets were selected from the batch of prepared tablets. A standard acidic solution, simulating the intragastric fluid (SGF), was prepared with a nearly constant viscosity of approximately 1 mPa·s. The SGF consisted of 900 mL of distilled water and 1.6 mL of 0.1 N HCL, achieving a pH of 1.2. The SGF was maintained at 37 ± 0.5 °C in a water bath for 30 min to ensure stability. Each tablet was individually placed into the SGF, and its buoyant properties were visually inspected. Two critical parameters were recorded: floating lag time (FLT) and total floating time (TFT).

Magnetic measurements were conducted using an automated ACB sensor. The MFDDSs were placed within a dedicated container containing 900 mL of a 0.1 N HCl solution at pH 1.2 to carry out this experiment. The ACB was affixed to support and positioned on a computerized XYZ table in front of the container. A software routine was developed to control scanning position and timing using Mach3 Professional 2.0 software (ArtSoft, Fayette, ME, USA). Data acquisition was executed by altering the sensor's position within a 13 × 13 cm grid marked on the container, with increments of 5 mm. Signals were obtained through an analog–digital board (NI PCI-6030E, National Instruments Inc., Austin, TX, USA) and LabView 2010 v 10.0 software (National Instruments Inc.). Image processing was carried out in the Python environment, and vertical fluctuation motion was observable, enabling the determination of the MFDDS floating lag time (FLT). Automated magnetic measurements were performed using ACB over 8 h. The area of the magnetic tablet was calculated through these scans.

2.5 In Vitro Studies

Studies on the floating lag time (FLT) of MFDDSs were conducted using a specifically designed testing apparatus, allowing for the control of medium pressure. The testing apparatus comprised a sealed 2 L Erlenmeyer flask fitted with a stopper and equipped with a manometer to control pressure conditions (magnetic stir bar, 50 rpm, 37 ± 0.5 °C). Simu- lated gastric fluids (pH = 1.2; 0.1 N HCl) with different viscosities (1, 50, 120, and 320 mPa·s) were used for FLT testing [33,47]. Based on previous studies [41], pressure values within the range found in the stomach were established for evaluation. Different pressures, including atmospheric pressure, an additional 150 mmHg, and another 300 mmHg, were applied to the testing apparatus to mimic the behavior of the stomach interior, characterized by gastric tone oscillation influenced by prandial state and compliance [40,61].

After the simulated gastric fluid and magnetic stir bar were added to the apparatus, a magnetic stirrer was used for rotation and temperature control of the medium. Following this procedure, the MFDDSs were inserted into the apparatus and the system was sealed. With the manometer attached, different pressures used in the study were applied. Tests were performed in triplicate for each applied pressure and different viscosity value, with the aim of evaluating the FLT.

2.6 In Vivo Study Protocol

Eight healthy volunteers (both sexes, aged between 18 and 30 years, body weight between 50 and 80 kg, and BMI < 22 kg/m^2) were enrolled. Exclusion criteria included regular use of drugs that may interfere with gastrointestinal motility or pH, like antiemetics, prokinetics, antibiotics, opioids, laxatives, and macrolides, pregnancy, smoking, abdominal surgery, chronic diseases, and any other disorders that may affect GI motility. Volunteers passed through an initial phase for gastric projection identification, which consisted of

scanning all gastric projections with a mono-channel ACB sensor until finding the high magnetic signal intensity point (stomach). This point was marked with x-y coordinates, setting the reference on the umbilical scar. The study covered two moments (prandial state) of GI motility: fasting and feeding, as it was a randomized and double-anonymized comparative study to evaluate the magnetic behavior of floating tablets. There was a 7-day period separating fasting and fed procedures for the same subject. After 8 h of overnight fasting, a magnetic floating tablet was offered to all volunteers with 200 mL of Del Valle® orange juice (fasting and fed states). In fed-state measurements, 30 min before taking the magnetic tablet, the volunteer received a standard meal consisting of 2 slices of Pullman® loaf bread and a slice of ham and mozzarella. The single-channel ACB sensor is based on a double magnetic flux transformer, with a pair of exciter/detector coils acting as reference and another as measurement, excited by a voltage of 20 V and a frequency of 10 kHz, with the output signal detected in a lock-in amplifier. The ACB sensor was positioned over the gastric projection region, performing continuous monitoring until the tablet fluctuated and reached the cecum (Figure 1). At the end of the procedure, volunteers received a standard lunch (Perdigão® lasagna with Del Valle® orange juice, Perdigão, Brazil).

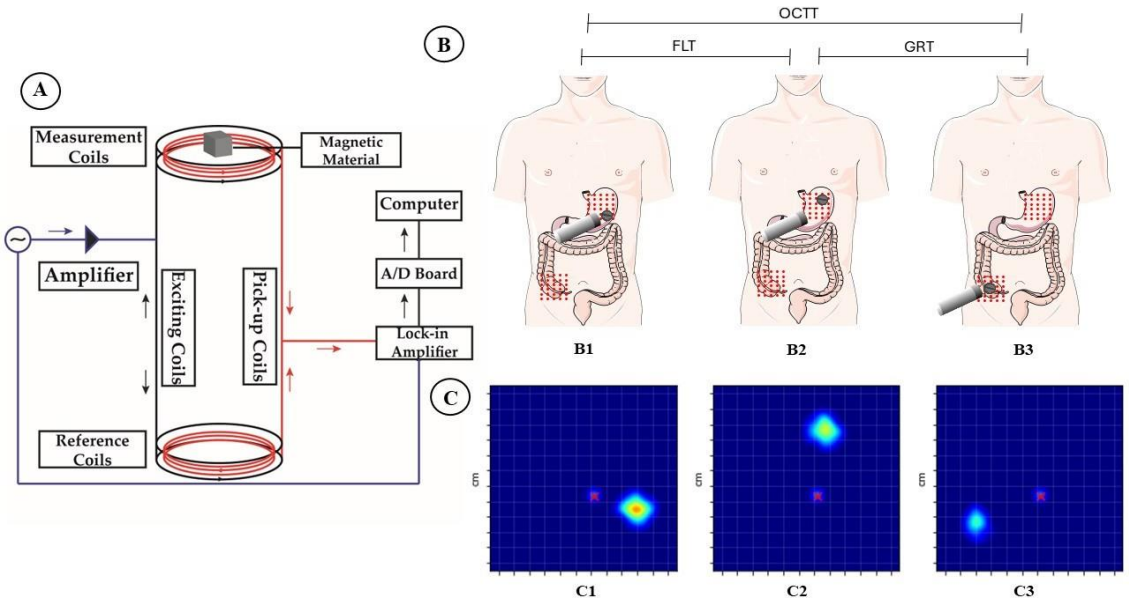

Figure 1. Schematic diagram of the *in vivo* study methodology. (**A**) Schematic representation of the Alternating Current Biosusceptometry (ACB) system. The red lines indicate the pickup coils, and the black lines indicate the excitation coils. (**B**) Region of the stomach and colon monitored by the ACB mono-channel system at three different moments: (**B1**) ingestion of the magnetic tablet; (**B2**) start of floating of the magnetic tablet; and (**B3**) arrival of the tablet in the colon. (**C**) Reconstructed image of the magnetic tablet at three different moments: (**C1**) ingestion of the magnetic tablet; (**C2**) start of floating of the magnetic tablet; and (**C3**) arrival of the tablet in the colon. Red dots represent each position measured on the abdominal surface, and red x represents the umbilical scar.

Floating lag time (FLT), gastric retention time (GRT), and orocaecal transit time (OCTT) were determined by scanning gastric projections in different regions [58,60]. By collecting data on magnetic field deformation intensity over time and registering it in a data matrix, images corresponding to the tablet's position at specific times can be obtained.

This study was approved according to the Ethics in Research of Botucatu Medicine School, São Paulo State University (UNESP) protocol and under the Declaration of Helsinki. All volunteers signed the Informed Consent Form before they participated in the study (Certificate of Presentation for Ethical Appreciation: 49323221.3.0000.5411).

2.7 Statistical Analysis

The experiments to evaluate the floating lag time (FLT) for different pressures and viscosities were represented using mean ± standard deviation. Gastrointestinal transit parameters were analyzed using a paired Student's *t*-test. We perform normality tests and ANOVA for multiple comparisons, revealing significant differences between the means of all parameters analyzed in the study. As a result, we performed the Tukey test to identify specific groups that presented statistical variations from each other. Magnetic signals were analyzed utilizing MatLab (MathWorks, Natick, MA, USA) and Origin software (Ver- sion 2016, OriginLab Corporation, Northampton, MA, USA). Data analysis and statistical procedures employed GraphPad Prism v 8.0.1 (GraphPad Software, La Jolla, CA, USA). Differences were considered significant when $p < 0.05$.

3. Results

3.1 In Vitro Studies

The pharmacotechnical evaluation of floating magnetic tablets was carried out as a primary test regarding the FLT and TFT parameters. The results were 5 ± 0.86 min and >24 h, respectively. This TFT demonstrates that the matrix tablets achieved stable fluctuation performance for a long time.

To evaluate the swelling of the tablets, an experiment was carried out involving scanning the tablets at different times using the single-channel ACB system. Figure 2 shows examples of the images obtained in this experiment and the results of the tablet's magnetic area quantification over time. This figure shows the image of a tablet immediately after being added to a specific liquid container (initial magnetic area—first point on the graph, shown in Figure 2 (a). Figure 2 (b) is the magnetic representation of the tablet after 8 h in a liquid medium. It can be noticed that the swell and fluctuation processes occurred, and the tablet is more significant in area than the initial one. Figure 2 (c) presents a graph of variation of the quantified magnetic area of the images obtained.

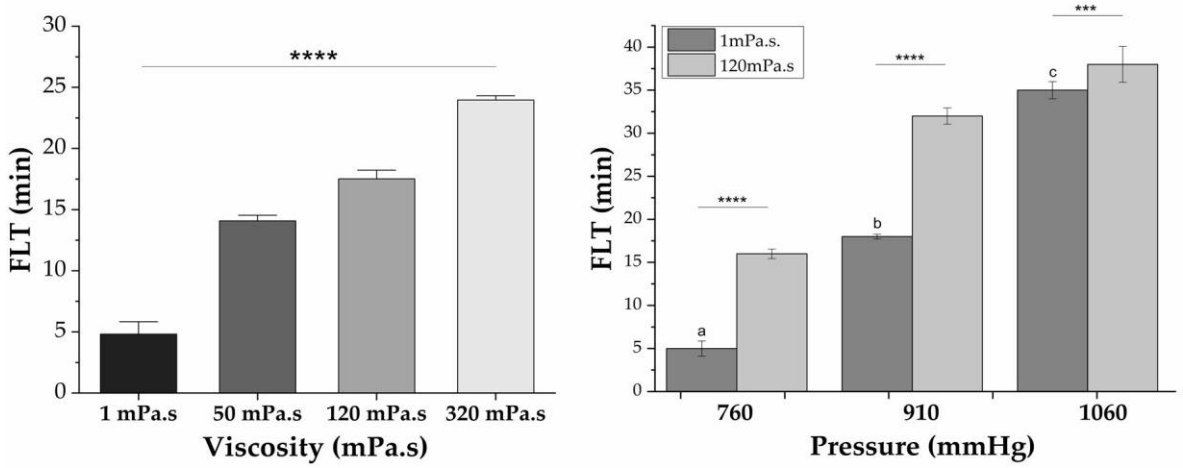

Figure 2. Magnetic image of the MDFFS before and after swelling and floating ((a), (b)). In (c), magnetic area variation over time graphic. *** $p < 0.001$, **** $p < 0.0001$.

The FLT was 6 ± 0.8 min, as illustrated in Figure 2 (c); an average exponential fitting provides a half-time ($T_{1/2}$—half the increase in area) of around 45 ± 7 min. The arrow indicates the FLT for this measurement.

Figure 3a shows the means and standard deviations (SDs) of the FLT for the different viscosities applied in the study (1, 50, 120, and 320 mPa·s) with pressure maintained at 760 mmHg. Figure 3b shows the different pressures applied in the study (760, 910, and 1060 mmHg), with viscosity held at 1 and 120 mPa·s. The FLT values in Figure 4a were 4.46 ± 0.88, 14.4 ± 0.65, 17.2 ± 0.61, and 24.1 ± 0.43. The FLT values for the medium

with a viscosity of 1 mPa·s when applying the different pressures were 5 ± 0.88 min, 18 ± 0.27 min, and 35 ± 1.0 min.

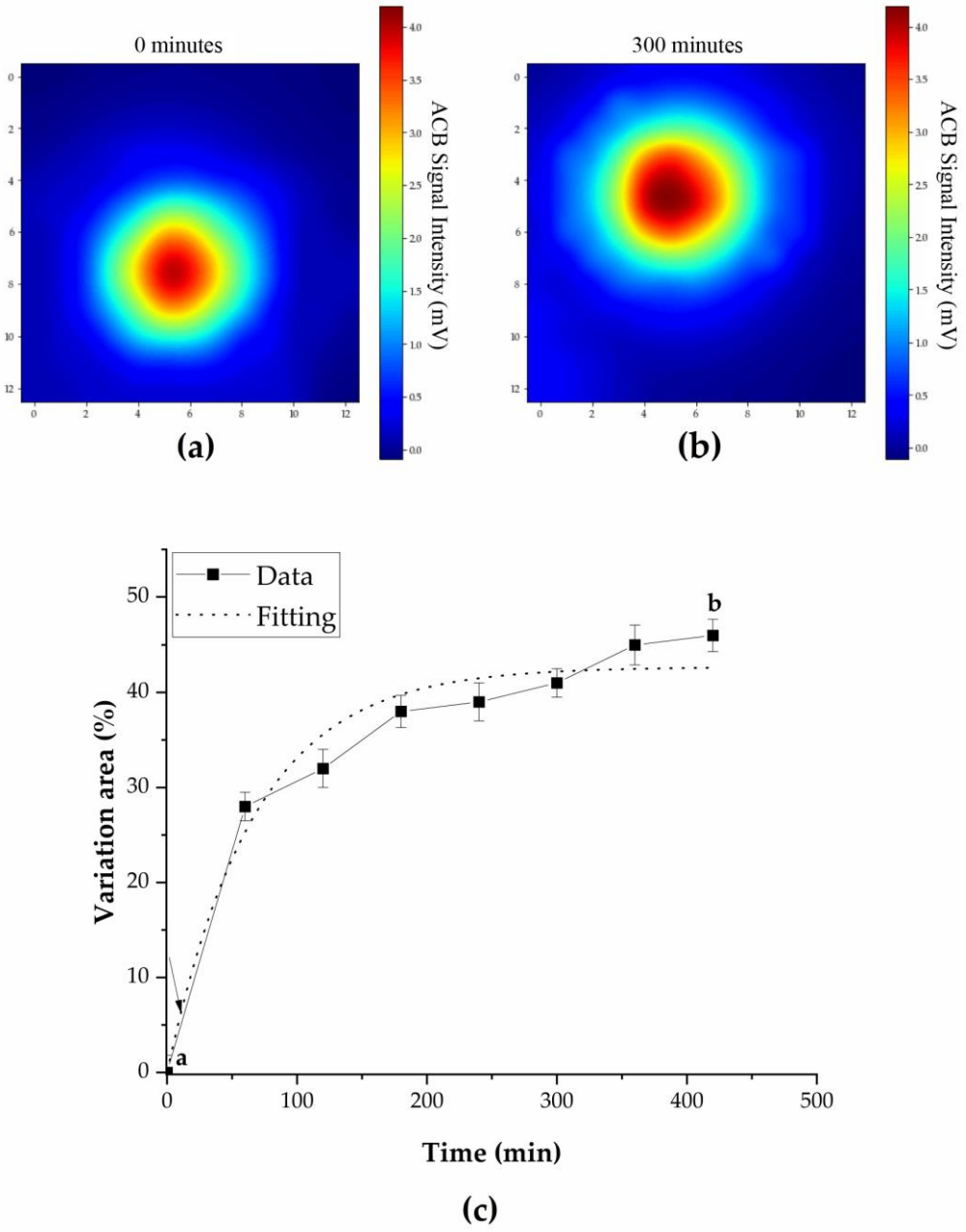

Figure 3. FLT of MFDDSs for different pressures (760, 910, and 1060 mmHg) and viscosities (1 and 120 mPa·s). Different letters indicate statistical differences between groups ($p < 0.05$). (**a**) First imaging, before fluctuation, right after positioning the tablet in the recipient; (**b**) Second imaging, after tablet's fluctuation; (**c**) Magnetic area increase of magnetic floating dosage form over time.

Comparing the times obtained at the same pressure, the increase in FLT differs with varying viscosity. In a possible situation close to the real one (viscosity of 120 mPa·s and pressure of 910 mmHg), the FLT value was 32 ± 0.93 min, 14 min more than in the situation with a viscosity of 1 mPa·s and pressure of 910 mmHg. For pressures of 760 and 1060 mmHg, the FLT was 16 ± 0.55 min and 38 ± 2.07 min, respectively.

The increase in FLT is observed with an increase in pressure, demonstrating the influ- ence of pressure on the time taken for the tablet to float after its insertion into the medium.

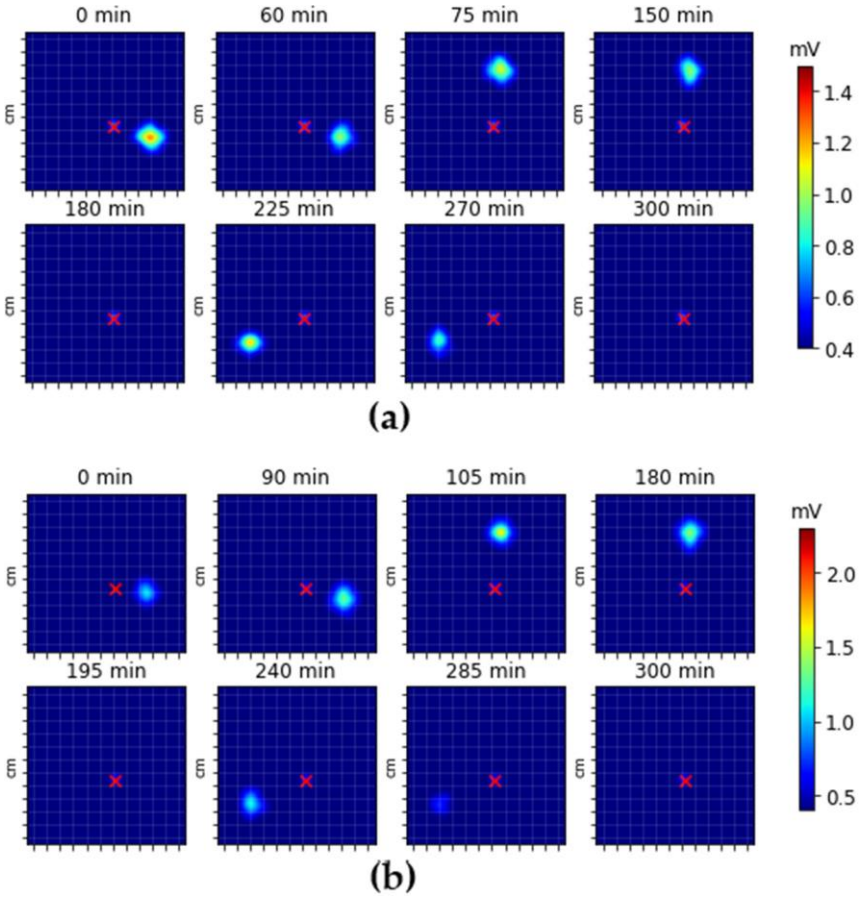

Figure 4. Magnetic real-time tracking, monitoring, and imaging of MFDDSs *in vivo* in two prandial states: fasting (**a**) and fed (**b**). The red cross indicates umbilical scar reference.

3.2 In Vivo Studies

Figure 4 shows sequential images of the fasting (Figure 4a) and fed (Figure 4b) states measured with volunteers. It is noticed that the FLT, GRT, and OCTT were modified due to the prandial state.

Table 1 illustrates the data obtained for eight healthy volunteers on gastrointestinal transit parameters (GRT and OCTT) and the FLT parameter evaluated in both prandial states (fasting and fed). The fasting group presented lower indices of the parameters assessed concerning the fed group. All results are presented as mean and standard deviation (SD).

Table 1. Comparison of gastrointestinal transit parameters in the group of fasting and fed volunteers. Different letters indicate statistical differences between groups ($p < 0.05$).

	Fasting			Fed		
Subjects	**GRT (min)**	**OCTT (min)**	**FLT (min)**	**GRT (min)**	**OCTT (min)**	**FLT (min)**
1	120	240	60	180	300	90
2	150	225	75	180	240	105
3	100	225	60	135	270	75
4	150	270	90	225	330	120
5	120	225	75	285	340	165
6	135	240	90	150	240	105
7	175	240	90	205	365	125
8	165	270	45	165	315	75
Mean	139.4 [a]	241.9 [a]	73.1 [a]	190.2 [b]	300 [b]	107.5 [b]
SD	25.3	18.7	16.9	47.7	46.4	29.8

This reinforces that in all measurements with volunteers, the floating state of the MFDDS was maintained, indicating that they presented good conditions for maintaining their purpose of floating. After FLT, the tablets continued to fluctuate until the complete retention time.

3. Discussion

Gastroretentive drug delivery systems (GRDDS) are ingeniously engineered to extend their residence within the stomach. This prolongation leads to an extended window during which drugs can be effectively absorbed, enhancing their bioavailability [62]. These systems offer several advantages for a spectrum of medications. For instance, drugs intended to act directly in the stomach, such as the antibiotic metronidazole used for *Helicobacter pylori* eradication [63] and those with limited absorption in the upper stomach or small intestine, like simvastatin [64] and norfloxacin [65]. Moreover, GRDDS are an optimal choice for drugs that are prone to degradation in the intestinal or colonic environments, such as captopril [66] and for substances with poor solubility under alkaline conditions, like diazepam [67]. Various strategies have been proposed to achieve gastric retention and prevent unpredictable dosages from emptying. These may involve the co-administration of drugs or pharmaceutical additives that modulate gastric motility patterns, thereby delaying gastric emptying.

Nevertheless, the study of the behavior of these GRDDS is essential given the possibil- ity of influence of pressure, viscosity, and prandial state. Furthermore, *in vivo* measure- ments configure a realistic situation of these formulations' behavior in the GIT.

One cost-effective technique for assessing formulation behavior in the GIT is the ACB system, which is sensitive and does not require electromagnetic shields. Studies have shown that the ACB system can determine the onset of the disintegration process of magnetic tablets coated with Eudragit E100 and under the influence of omeprazole by acquiring images of the volunteer's stomach at different times. In another study, simultaneous image acquisition and calculation of the area increase made it possible to observe the difference in the disintegration process between volunteers who received placebo tablets and those who received prucalopride. Therefore, the system effectively monitors and locates magnetic tablets, enabling the delimitation and understanding of the processes that occur in the GIT. In this study, we aimed to obtain *in vitro* behavior of an MFDDS (swelling and floating lag time) in the face of different pressures and viscosities and *in vivo* (floating lag time, gastric retention time, and orocaecal transit time) in the fasting and fed state.

Figure 2 illustrates the behavior of the increase in area of the formulation due to the swelling process and concomitant water uptake. We quantified the average T(1/2) values, in which we considered time to reach 63% stabilization in the magnetic area increase curve with an average and standard deviation of 170 ± 15, indicating an extended time window of formulation dynamics. It is important to note that Corá et al. found a direct relationship between an increase in surface area and dissolution while using a different type of magnetic solid dosage form [68]. These measurements provide further evidence of the reliability of the biomagnetic technique in assessing the changes over time in the magnetic field distribution sensor (MFDDS) area. The effectiveness of MFDDS is affected by pressure and viscosity; by evaluating TFT and FLT in different viscosity/pressure combinations and under controlled situations (water and ambient pressure), the impact of these factors can be better understood.

Figure 3a illustrates a tablet's FLT concerning the medium's viscosity. A significant positive correlation between the medium's viscosity and FLT is evident, indicating that as viscosity increases, so does the time to start the floating process (FLT). This phenomenon can be attributed to the increased resistance that a more viscous medium offers to the downward movement of the tablet, thereby prolonging its FLT. In addition, the increase in FLT is likely due to the differing ionic strength values (0.4 M versus 0.18 M) presented by the media with viscosities of 1 mPa·s and 120 mPa·s, respectively. This difference in

ionic strength results in a decreased water permeation rate through the tablet, consequently leading to a higher FLT [69].

Figure 3b presents an examination of the floating lag time (FLT) of a tablet in two different medium viscosities (1 and 120 mPa·s) under three distinct pressures (760, 910, and 1060 mmHg). The results depicted a clear trend that the FLT increases with pressure, a phenomenon more pronounced for the medium with a viscosity of 120 mPa·s. The FLT difference between the two viscosities is particularly noticeable at the lowest pressure (760 mmHg), where the FLT for 120 mPa·s is significantly higher. As the pressure increases, the difference in the tablet's floating ability becomes smaller but remains significant. This can be seen as a connection between the viscosity and pressure of the medium and the tablet's floating behavior. When pressure increases, the tablet may float better in more viscous media. It is possible that the physical properties of the medium and the tablet change under high-pressure conditions. These insights suggest that both the viscosity of the medium and the pressure play pivotal roles in determining a tablet's FLT. Therefore, meticulous consideration of these factors is necessary when designing and optimizing tablet formulations to ensure adequate flotation and, consequently, controlled drug release.

In this study, the profile of MFDDS in the gastrointestinal tract (GIT) was assessed through *in vivo* acquired images. Figure 3b showed a significant increase in FLT (floating lag time) in the range of 50 to 120 mPa·s, which is more representative of real situations [49]. This increase may cause rapid emptying of the floating tablet into the duodenum, prevent- ing it from achieving its greater purpose of retention and prolonged release. The significant increase in FLT is because the more viscous medium slows down the diffusion of water into the tablet, which delays the beginning of swelling and gel formation, which reduces the tablet's density [70,71]. In addition, the tablet's ability to react with gastric acid and produce carbon dioxide is slowed down by the food in the stomach. As a result, the time it takes for the tablet to dissolve varies greatly, depending on the type of food consumed,
especially during the postprandial state.

Table 1 shows the GRT, OCTT, and FLT parameters obtained after processing the *in vivo* images. It was observed that the fasting group exhibited lower GRT, OCTT, and FLT values compared to the fed group. It is important to highlight that, under fasting conditions, the viscosity in the stomach remains at its basal state of 1 mPa·s, indicating an accelerated contractile activity in the stomach and, consequently, the potential for rapid tablet emptying [45,72].
In the fed group, the increase in the analyzed parameters is associated with the elevated viscosity in the stomach after the ingestion of food, related to an increase in intragastric pressure. The influence on the viscosity of the medium leads to interactions between the various excipients in the tablet formulation and the food bolus (proteins, fat, sugar), forming a hydrophobic barrier arounsd the tablet. This barrier affects the diffusion rate of gastric fluid into the tablet, causing a delay in the formation of the gelled layer and the release of carbon dioxide and, consequently, a delay in FLT, GRT, and OCTT [69].

4. Conclusions

Gastroretentive drug delivery systems, specifically floating systems, are an attractive solid pharmaceutical form because they can float and extend the time drugs stay in the stomach, allowing for controlled and site-specific drug delivery.

Using the ACB technique, it was possible to monitor MFDDSs *in vitro* and inside the GIT. The impact of pressure and viscosity on MFDDSs *in vitro* was evaluated. The results showed a significant direct relationship between pressure, viscosity, and MFDDS.

In terms of *in vivo* measurements, it was observed that the prandial state affects fluctuation and physiological parameters such as gastric retention time (GRT) and overall transit time (OCTT), significantly delaying them.
The ACB system has demonstrated its effectiveness in real-time monitoring, tracking, and imaging of MFDDSs, thereby establishing itself as a valuable technique for evaluating the behavior of floating delivery systems in the gastrointestinal tract. This may be useful

in developing new drug delivery systems that can effectively target specific areas of the gastrointestinal tract, improving the efficiency of drug delivery outcomes.

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Capitulo 2

Abstract

In recent decades, the development of effective therapies with minimal adverse effects has become a major challenge in the pharmaceutical field. Despite its popularity, oral administration faces limitations related to the physiological variability of the gastrointestinal tract (GIT), such as gastric emptying time, absorption window, and site of drug release. In this context, modified-release systems—especially gastroretentive drug delivery systems (GRDDS)—have gained prominence. GRDDS aim to prolong gastric retention time (GRT), facilitating controlled and localized drug release, particularly beneficial for drugs with limited absorption windows or instability in alkaline pH. This study evaluated the *in vivo* performance of a magnetic floating drug delivery system (MFDDS) containing metronidazole using pharmacomagnetography based on alternating current biosusceptometry (ACB) in healthy volunteers (n=12, aged 19-21 years) under fasted and fed conditions. Results demonstrated that the prandial state significantly influenced MFDDS behavior, with food intake prolonging both the floating lag time (FLT) (105-120 min fed vs. 45-60 min fasted) and gastric retention time (GRT) (165.0 ± 32.2 min fed vs. 118.3 ± 35.3 min fasted, $p<0.0001$). The orocecal transit time (OCTT) was similar between groups (271.7 ± 32.0 min fed vs. 254.2 ± 44.9 min fasted, $p>0.05$), while small intestine transit time (SITT) was shorter in the fed state (111.7 ± 22.3 min) compared to the fasted state (140.0 ± 47.7 min), though not statistically significant. Pharmacokinetic parameters showed significant differences, with the fed state resulting in delayed time to maximum concentration ($Tmax$) (252.0 ± 52.9 min fed vs. 174.0 ± 60.0 min fasted, $p<0.05$) but substantially higher maximum plasma concentrations (Cmax) (11.0 ± 5.7 µg/mL fed vs. 4.7 ± 2.2 µg/mL fasted, $p<0.05$) and area under the curve (AUC360) (2606.1 ± 1825.5 µg·h/mL fed vs. 969.3 ± 638.3 µg·h/mL fasted, $p<0.05$). The time lag before detectable plasma concentration ($Tlag$) was similar between groups (67.5 ± 21.8 min fed vs. 86.7 ± 31.4 min fasted, $p>0.05$). The increased viscosity of gastric contents in the fed state delayed the initial tablet flotation by forming a hydrophobic barrier around the tablet, restricting gastric fluid diffusion into the polymeric matrix. This extended gastric retention in the fed state resulted in more complete and sustained metronidazole absorption, confirming the effectiveness of the gastroretentive system in optimizing drug bioavailability, particularly when administered after meals.

Keywords: Gastroretentive drug delivery systems; Pharmacomagnetography; Metronidazole; Alternating current biosusceptometry; prandial state; Bioavailability.

1. Introduction

In recent decades, the development of effective therapies with minimal adverse effects has become a major challenge in the pharmaceutical field. In this context, the industry has invested in innovative drug delivery systems, taking into account factors such as the dosage form, excipients, physicochemical properties of the active pharmaceutical ingredient, and the route of administration. The oral route stands out due to its simplicity, low cost, and high patient acceptance, accounting for more than half of the marketed formulations[1, 2].

Despite its popularity, oral administration faces limitations related to the physiological variability of the gastrointestinal tract (GIT), such as gastric emptying time, the absorption window, and the site of drug release. Many drugs are primarily absorbed in the upper small intestine and may be poorly absorbed or degraded throughout the GIT. In this context, modified-release systems—especially gastroretentive drug delivery systems (GRDDS)—have gained prominence[3, 4].

GRDDS aim to prolong gastric retention time (GRT), facilitating controlled and localized drug release. These systems are particularly beneficial for drugs with a limited absorption window, instability in alkaline pH, or local action in the stomach. Strategies employed include floating, bioadhesive, expandable and magnetic retention mechanisms[5-7].

Floating systems are widely studied due to their ability to remain suspended in gastric contents and being emptied last, extending GRT and optimizing drug release. They are classified into effervescent systems, which produce CO_2 upon contact with gastric acid, and non-effervescent systems, based on hydrophilic polymers that expand with gastric fluids. Both approaches aim to reduce the relative density of the dosage form, maintaining it within the gastric region.

Extending GRT offers important clinical benefits: it improves the bioavailability of drugs with restricted absorption, stabilizes plasma levels, reduces adverse effects, and increases treatment adherence. Drugs such as metronidazole, ranitidine, levodopa, ciprofloxacin, furosemide, and gabapentin are examples of substances that benefit from this technology[8, 9].

Among clinical applications, the treatment of *Helicobacter pylori* infections stands out, a bacterium associated with various gastrointestinal diseases, such as ulcers and gastric cancer. GRDDS use has proven effective in ensuring localized and prolonged antibiotic release in the stomach.

The effectiveness of GRDDS is influenced by physiological factors, particularly gastric motility regulated by the migrating motor complex (MMC), which is active during fasting and suppressed postprandially[10]. The MMC comprises four phases of peristaltic activity, with phase III being the most likely for expelling solid dosage forms. Interindividual variability of the MMC presents a challenge for the predictability of GRDDS. Therefore, detailed knowledge of gastric physiology is essential for developing systems effectively adapted to patient profiles[11, 12].

Thus, evaluating GIT motor function in the context of drug absorption is essential and may significantly impact drug bioavailability. Therefore, simultaneous monitoring of pharmacokinetic parameters, motility and localization da FFS are important.

Several non-invasive monitoring methods using magnetic resonance imaging and superconducting interference devices have been employed to assess GIT. Among these, the monitoring of magnetic markers (MMM) has gained attention. When MMM is combined with pharmacokinetic data, the method is referred to as pharmacomagnetography (PMG). This approach provides valuable information on the relationship between drug absorption from pellets and their transit through the GIT[13, 14].

The alternating current biosusceptometry (ACB) system is an alternative biomagnetic technique for evaluating GRDDS in PMG studies. ACB measures the magnetic susceptibility of magnetic markers and GRDDS using alternating magnetic fields, offering real-time information on their transit through the GIT. The ACB technique provides real-time imaging of biological systems, allows for the monitoring of changes over time, is non-invasive, does not require a magnetically shielded environment, is portable, does not use ionizing radiation and has a lower cost compared to other imaging techniques[15-18].

In summary, gastroretentive drug delivery systems represent a promising strategy to overcome the physiological barriers of the GIT and enhance the therapeutic performance of various drugs, particularly those with low solubility, instability in alkaline pH, or absorption limited to the stomach and the proximal small intestine.

This study aimed to use pharmacomagnetography to evaluate the gastrointestinal transit and pharmacokinetic profile of a floating magnetic prolonged-release tablet administered to healthy volunteers under different prandial states (fasted/fed). A study was performed using metronidazole as a model drug using pharmacomagnetography evaluation based on the ACB technique.

2. Materials and methods

2.1 Materials

For manufacture of the floating magnetics tablets, the following materials were used: Ferrite powder ($MnFe_2O_4$; diameter between $50 < \varphi < 75\ \mu m$) from Thornton (Vinhedo, Brazil) as the magnetic marker; (HPMC, Methocel®), kindly provided by Colorcon (Cotia, Brazil); lactose, (PVP K30), magnesium stearate, and sodium starch glycolate were obtained from Henrifarma (São Paulo, Brazil); hydroxyethyl cellulose (HEC) from Colorcon (Indaiatuba, Brazil); and sodium bicarbonate from Audaz (São Paulo, Brazil). All other reagents and solvents were of analytical grade.

2.2 Floating Magnetic Tablets and Control Quality

The tablets used in this study were previously described by Rodrigues et al. (2024)[7], composed of manganese ferrite powder (430 mg, 35.83%), magnesium stearate (18 mg, 1.5%), hydroxypropyl methylcellulose (HPMC E4M—430 mg, 35.83%), lactose (152 mg, 12.6%), polyvinylpyrrolidone (PVP K30) (10 mg, 0.83%), and sodium bicarbonate (160 mg, 13.3%). The excipients were mixed, and the tablets were manually produced using a single punch machine (Erweka, EKO™, Langen, Germany) with a flat face and 12 mm diameter, under a pressure of 30 kN, resulting in tablets weighing 1.2 g. The magnetic floating drug delivery system (MFDDS) was tested according to the procedures outlined in the US Pharmacopeia, evaluating average weight, hardness, and friability. Complete preparation details are available in Rodrigues et al. (2024)[7].

2.3 *Alternating Biosusceptometry Current (ACB)*

The ACB system operates as a double magnetic flux transformer composed of two pairs of coils, with the pair furthest from the sample acting as a reference system and the pair closest to the sample acting as a measurement system, with the detector coils arranged in a first-order gradiometric[19-22]. When magnetic material is brought close to the measurement system, an imbalance in the magnetic flux occurs and an increase in the electrical signal can be observed. Detailed technical information was previously reported by Corá et al. (2010)[23].

2.4 In vivo Protocol

The study included twelve healthy volunteers aged between 19 and 21 years, without motor dysfunctions or regular use of medications that could interfere with gastrointestinal transit. All participants were duly informed about the procedures and objectives of the research, signing the Free and Informed Consent Form (FICF), in accordance with the terms established by the Research Ethics Committee of the Botucatu School of Medicine (REC-BSM) under protocol CAAE: 49323221.3.0000.5411. The volunteers attended the Biomagnetism Laboratory on two separate occasions, once in the fasting and once in the fed state.

2.4.1 *Phase I – ACB Monitoring: Prandial State – Fasting*

In this first stage, participants were instructed to fast for eight hours. A $13\ x\ 13$ grid of points was drawn in the gastric projection and the cecal region (point of McBarney). At the beginning of the procedure, each participant ingested a magnetic tablet with 200 mL of water. With the aid of the ACB sensor, the region over the gastric and cecal projection was mapped, recording the x and y coordinates in relation to the umbilical scar. Fifteen minutes after tablet ingestion, ACB monitoring began at 15-minute intervals, with venous blood collection every hour. After the tablet passed from the stomach to the duodenum (GRT), a standard meal was offered, consisting of Perdigão® lasagna (600g) and Del Valle® orange juice. The nutritional information of the foods offered is detailed in Appendices 1.

2.4.2 *Phase II – ACB Monitoring: Prandial State – Fed*

As in Phase II, participants were instructed to fast for eight hours prior to the procedure. However, upon arrival at the procedure site, they were offered a standardized snack consisting of 50 g of Seven Boys® sliced bread, 40 g of Perdigão® pork ham, and 30 g of Sadia® mozzarella cheese, providing approximately 264 kcal. The tablet was administered along with 200 mL of Del Valle® orange juice, which contributed an additional 84 kcal and 38 mg of vitamin C (see Appendices 1 – Nutritional Information of Foods Offered).

Following ingestion (fifteen minutes), ACB monitoring was initiated at 15-minute intervals, while venous blood samples were collected every 60 minutes. As in Phase II, once the tablet was identified in the duodenum (after GRT), participants were offered the same food offered in phase I. This allowed for the estimation of key gastrointestinal transit parameters: floating lagtime (FLT) Gastric Retention Time (GRT), Orocecal Transit Time (OCTT), and Small Intestine Transit Time (SITT) — the latter calculated as the difference between OCTT and GRT.

2.5 Bioavailability of Metronidazole

2.5.1 Analytical Methodology and Processing of Plasma Samples

The quantification of serum metronidazole during *in vivo* analyses was performed by Ultra High-Performance Liquid Chromatography (UHPLC). To obtain the standard curve, known concentrations of metronidazole (0; 0.1; 0.2; 0.5; 1; 2.5; 5 and 10 µg/mL) were prepared from fractional dilutions of a fortification solution (metronidazole 10 µg/mL) in 500 µL of plasma. Subsequently, 2 mL of acetonitrile were added to each sample, which were centrifuged at 4500 rpm and 4ºC for 10 minutes. The supernatant was transferred to 15 mL falcon tubes, frozen at -80ºC, and subjected to lyophilization overnight. The following day, the samples were reconstituted using a water: methanol solution (90:10, v/v), transferred to Eppendorf tubes, centrifuged at 14000 rpm, 4°C for 10 minutes, and the supernatant was transferred to the analysis vial and injected into the chromatography equipment.

Metronidazole was extracted from the volunteers' plasma samples following the protocol established by Pires (2020)[24]. 2 mL of acetonitrile were added to 500 µL of plasma, the samples were centrifuged at 4500 rpm, 4ºC for 10 minutes, and the supernatant was transferred to 15 mL falcon tubes. The samples were then frozen at -80ºC and subjected to lyophilization overnight. The next day, the lyophilized samples were reconstituted with water: methanol solution (90:10, v/v), transferred to Eppendorf tubes, and centrifuged at 14000 rpm, 4ºC for 10 minutes. The supernatant was transferred to the analysis vial and injected into the chromatography equipment for quantification.

2.6 Statistical analysis

Data are presented as the mean ± standard deviation (SD). Magnetics and pharmacokinetic parameters were compared between both treatments using the paired Student t-test. Values of $p < 0.05$ were considered statistically significant. All data analysis and statistics were performed with GraphPad Prism (GraphPad Software, La Jolla, USA).

3. Results and discussion

Gastroretentive Drug Delivery Systems (GRDDS) aim primarily to increase the gastric retention time (GRT) of pharmaceutical formulations. Prolonging the residence time of the dosage form in the upper gastrointestinal tract (GIT) enhances drug absorption and contributes to improved bioavailability[25, 26] .

Evaluating the behavior of GRDDS is essential, considering the influence of physiological factors such as pressure, viscosity, and prandial state. Rodrigues et al. assessed magnetic floating drug delivery systems (MFDDS) under various simulated physiological parameters, including pressure and viscosity. *In vitro* tests demonstrated that factors such as pressure, viscosity, and floating lag time (FLT) directly affect drug behavior in the GIT. The profile of MFDDS in the gastrointestinal tract was also evaluated through *in vivo* imaging using Alternating Current Biosusceptometry (ACB).

In the present study, pharmacomagnetography based on ACB was employed to evaluate the gastrointestinal transit of GRDDS, along with the *in vivo* drug release and absorption processes of metronidazole. A correlation was established between the site of drug release (monitored magnetically) and absorption (assessed pharmacokinetically) under different prandial states (fasted and fed).

In all volunteers evaluated in the two different prandial situations (fast and fed), it was possible to observe the floating behavior of GRDDS and its pellet behavior (magnetic marker) until it exited the stomach, showing good performance as a tablet in matrix form throughout the entire residence time in the stomach and arrival caecum.

Figures 1A and 1B display magnetic monitoring obtained via ACB, illustrating the localization and intensity of the GRDDS magnetic signal over 300 minutes in fed and fasted states, respectively (see Appendices 2 – Magnetic real-time tracking, monitoring, and imaging of grdds *in vivo* in two prandial states). According to the parameters obtained through pharmacomagnetography, evaluating the Floating Lag Time (FLT) for all

volunteers and measurements performed (Figure 1A and 1B) was possible. FLT was evaluated by modifying the position of GRDDS as observed in Figure 1A and 1B at times between 105 and 120 min (fed) and 45 and 60 min (fast) FLT was found to be increased in the fed group compared to the fasting group. This parameter is more directly associated with the viscosity of the gastric contents rather than with gastric motility itself. Food intake delays gastric emptying, which can increase pressure within the stomach; however, more significantly, it increases the viscosity of the gastric contents. This heightened viscosity impairs the immediate flotation of the tablet, as it alters the physicochemical interactions between the formulation's excipients and the constituents of the food bolus, including proteins, lipids, and carbohydrates[27-30].

These interactions lead to the formation of a hydrophobic barrier around the tablet, significantly restricting the diffusion of gastric fluids into the polymeric matrix. This phenomenon results in delayed gel layer formation and, subsequently, in delayed carbon dioxide release — the mechanism responsible for reducing the tablet's density below that of gastric fluid. Consequently, this delay prolongs the onset of tablet flotation (FLT), gastric retention time (GRT), and orocecal transit time (OCTT)[31-33].

Figure 1 presents a representative example of a volunteer undergoing tracking, monitoring, and real-time magnetic imaging of a GRDDS *in vivo* in two prandial states (fasted and fed), in the context of pharmacomagnetography. The results for the other volunteers are provided in the Appendices 2. In the fed state (Figure 1A), the magnetic signal remains concentrated in a relatively fixed region for an extended period, suggesting effective gastric retention, i.e., increased GRT[34-36]. In contrast, in the fasted state (Figure 1B), the signal appears to disperse or move more rapidly from the initial region, indicating accelerated gastrointestinal transit and a consequently shorter gastric retention time. This difference is physiologically expected, as the presence of food in the stomach delays gastric emptying[14-16, 37].

The correlation between GRDDS localization monitored by ACB (pharmacomagnetography) and metronidazole absorption (pharmacokinetics) is illustrated in Figure 1C. Plasma concentration curves of metronidazole reveal significant differences between the fed and fasted states. In the fed state, although initial absorption may appear slightly slower, plasma concentrations of metronidazole reach higher levels ($Cmax \approx 16\ \mu g/mL$) and remain elevated for a longer duration. This indicates more complete absorption due to prolonged GRDDS residence in the stomach, enabling

continuous drug release in a high-absorption region. Conversely, in the fasted state, absorption appears to begin more rapidly, but the peak plasma concentration is considerably lower ($Cmax \approx 7\ \mu g/mL$) and declines earlier[7, 38-40]. This suggests that rapid gastric emptying limits the time available for drug release and absorption in the upper GIT, resulting in reduced bioavailability[25, 41].

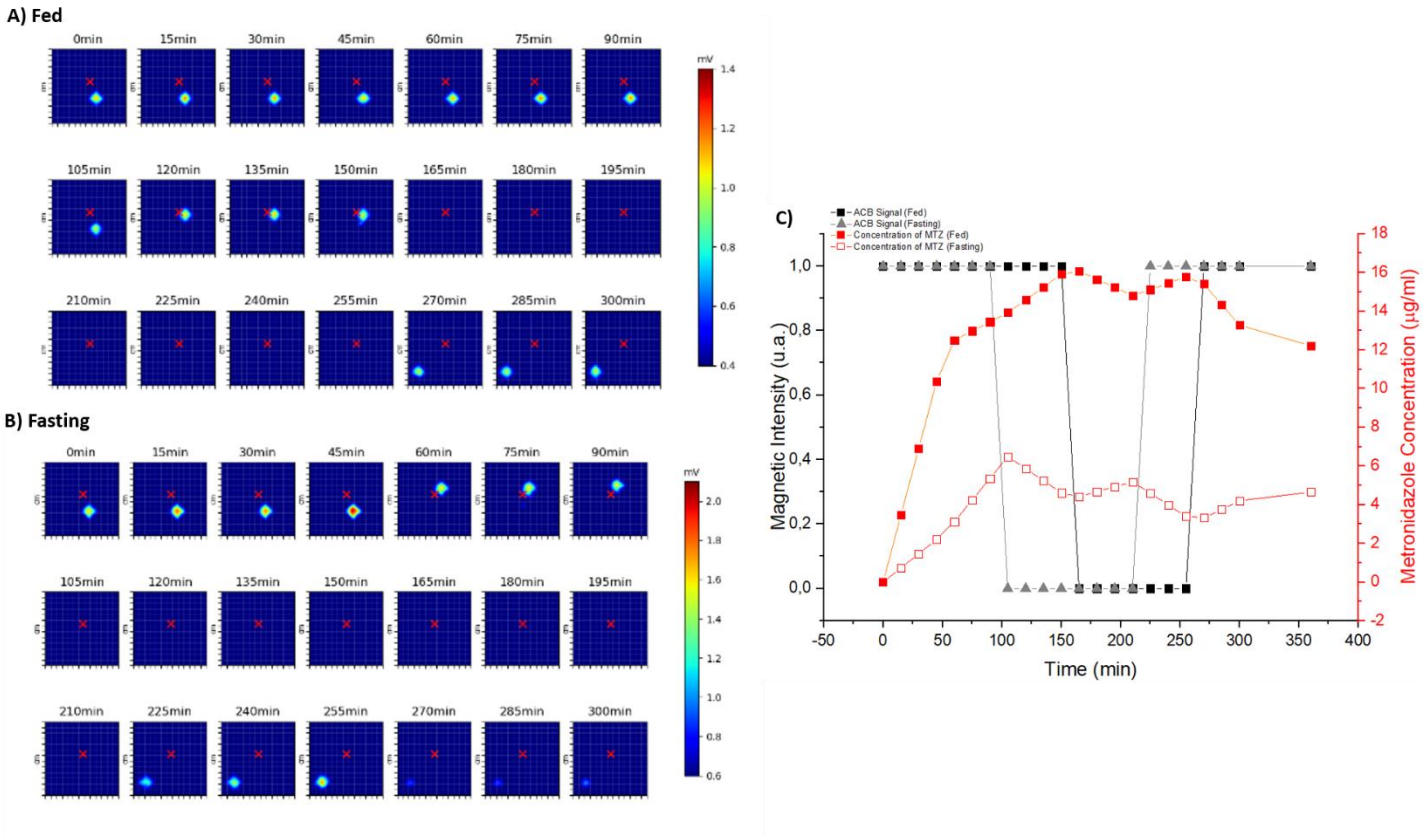

Figure 1. Magnetic real-time tracking, monitoring, and imaging of GRDDS *in vivo* in two prandial states: (A) fed (FLT=105 min and GRT=150 min) and (B) fasting (FLT=45 min and GRT=90 min).The red cross indicates umbilical scar reference. (C) Pharmacomagnetography analysis showing the gastrointestinal transit (black line) and drug release (red line) from a magnetic tablet.

According to the parameters obtained through pharmacomagnetography, it was possible to evaluate the Floating Lag Time (FLT) for all volunteers and measurements performed (Figure 2A). FLT was found to be increased in the fed group compared to the fasting group. This parameter is more directly associated with the viscosity of the gastric contents rather than with gastric motility itself. Food intake delays gastric emptying, which can increase pressure within the stomach; however, more significantly, it increases the viscosity of the gastric contents. This heightened viscosity impairs the immediate flotation of the tablet, as it alters the physicochemical interactions between the formulation's excipients and the constituents of the food bolus, including proteins, lipids, and carbohydrates.

These interactions lead to the formation of a hydrophobic barrier around the tablet, significantly restricting the diffusion of gastric fluids into the polymeric matrix. This phenomenon results in delayed gel layer formation and, subsequently, in delayed carbon dioxide release — the mechanism responsible for reducing the tablet's density below that of gastric fluid. Consequently, this delay prolongs the onset of tablet flotation (FLT), gastric retention time (GRT), and orocecal transit time (OCTT).

Regarding gastric retention time (GRT) (Figure 2B), it was significantly shorter in the fasting group compared to the fed group ($p < 0.0001$). This can be explained by the fact that under fasting conditions, gastroretentive dosage forms — like other indigestible solid materials — tend to remain in the stomach for no more than two hours. They are rapidly emptied by the action of the migrating myoelectric complex (MMC), potentially passing through the absorption window in the proximal small intestine while still releasing the drug in a sustained manner. As a result, they spend less time in the region with the highest concentration of absorption sites, leading to reduced drug absorption[42, 43].

However, when gastroretentive dosage forms are administered in the fed state, GRT becomes primarily dependent on the FLT of the dosage form, as well as on the composition and caloric content of the meal[26, 44]. The presence of food delays gastric emptying, allowing the tablet to remain in the stomach for a prolonged period. Floating dosage forms stay away from the pylorus, which is typical of floating, too are often retropropelled from the pyloric antrum back to the gastric body to undergo additional digestion, being released only at the end of the digestive phase or during the next MMC "housekeeper wave." This prolonged gastric retention time favors the controlled release of metronidazole, ensuring drug availability within the optimal absorption window and resulting in increased absorption in the small intestine[45-47].

In Figure 2D, the orocecal transit time (OCTT) was approximately equal between the fasting and fed groups, with no significant difference observed between the two study phases. The small intestine transit time (SITT) was longer in the fasting state compared to the fed state, although the difference was not statistically significant (Figure 2C). This may be directly related to the reduced GRT in the fasting state, which is influenced by increased gastrointestinal motility under these prandial conditions[5, 39, 48, 49].

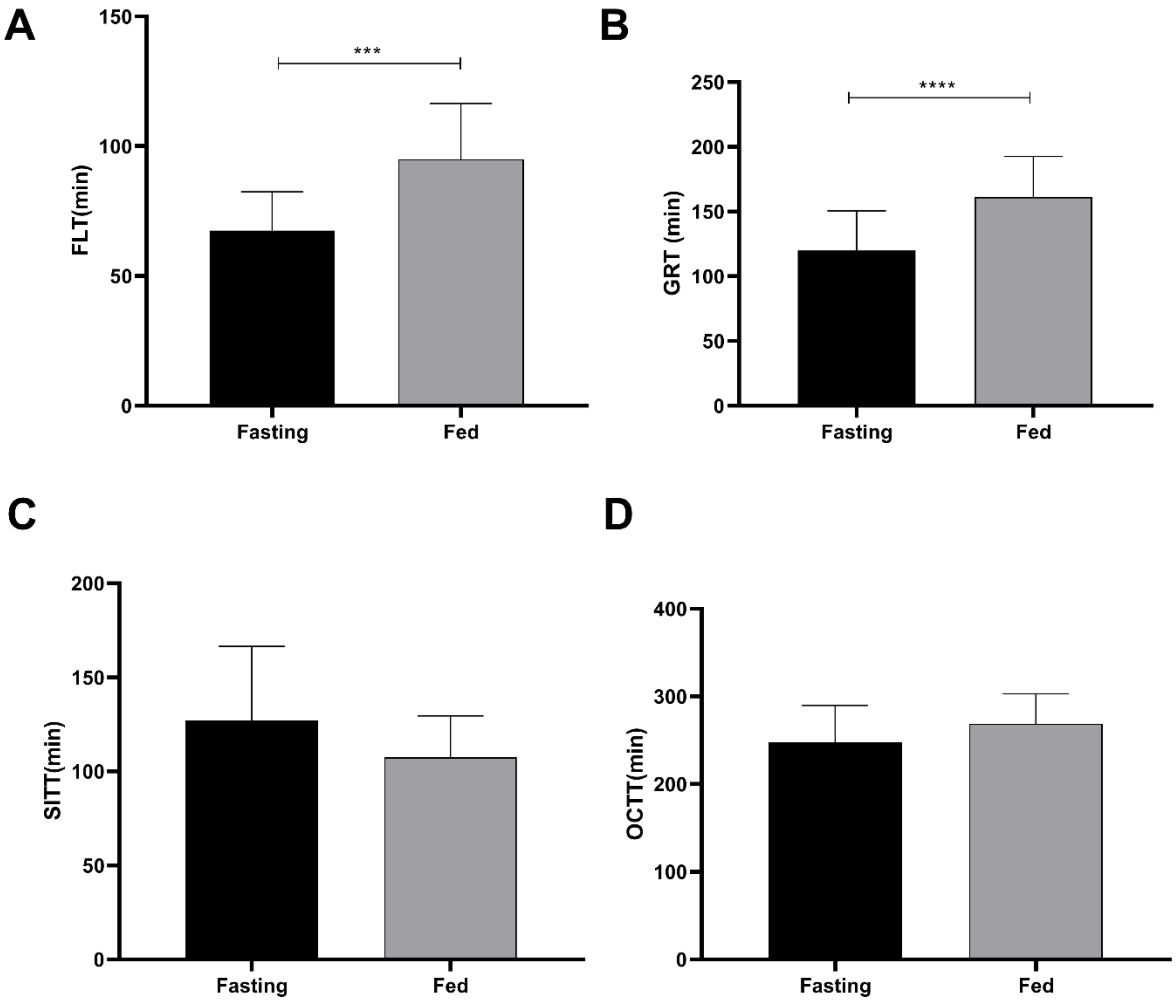

Figure 2. Gastrointestinal transit parameters evaluated *in vivo*.(A) Floating lag time, (B) gastric retention time, (C) small intestine transit time, and (D) orocecal transit time. Data are presented as mean ± standard deviation. ***p < 0.001, ****p < 0.0001.

Regarding the pharmacokinetic parameters analyzed, $Tlag$ was shorter in the fed group compared to the fasting group (Figure 3A). This suggests that drug release occurred more rapidly in fed volunteers than in fasting ones. However, the difference between the groups was not statistically significant[13, 50-52]. A possible explanation for this result lies in the blood sampling interval, which was conducted every hour. We believe that shorter intervals between blood collections could have allowed for a more accurate detection of differences in $Tlag$, thus providing a more precise result.

In Figure 3B, it can be observed that $Tmax$ was significantly longer in the fed group compared to the fasting group, indicating that it took more time for metronidazole to reach its maximum plasma concentration in the fed state, related to the increase in FLT.

Despite this delay in absorption, the $Cmax$ (maximum plasma concentration) was also higher in the fed group, suggesting that the presence of food increases the bioavailability of metronidazole at the site with a higher density of absorption receptors, thereby enhancing its uptake[53, 54].

Moreover, the AUC (area under the concentration-time curve) was also higher in the fed group, indicating an overall increase in metronidazole bioavailability. This enhanced bioavailability is associated with the increased gastric retention time (GRT), as assessed by ACB, which prolongs the drug's contact with the absorption sites in the gastrointestinal tract. The higher viscosity of gastric contents in the presence of food also contributes to a more controlled and sustained drug release due to higher GRT, maintaining the drug in the absorptive regions, particularly the proximal small intestine, for a longer duration. Consequently, slower transit through the upper gastrointestinal tract may favor the tablet's residence in this region, thereby enhancing absorption efficiency[7, 14-16, 55, 56].

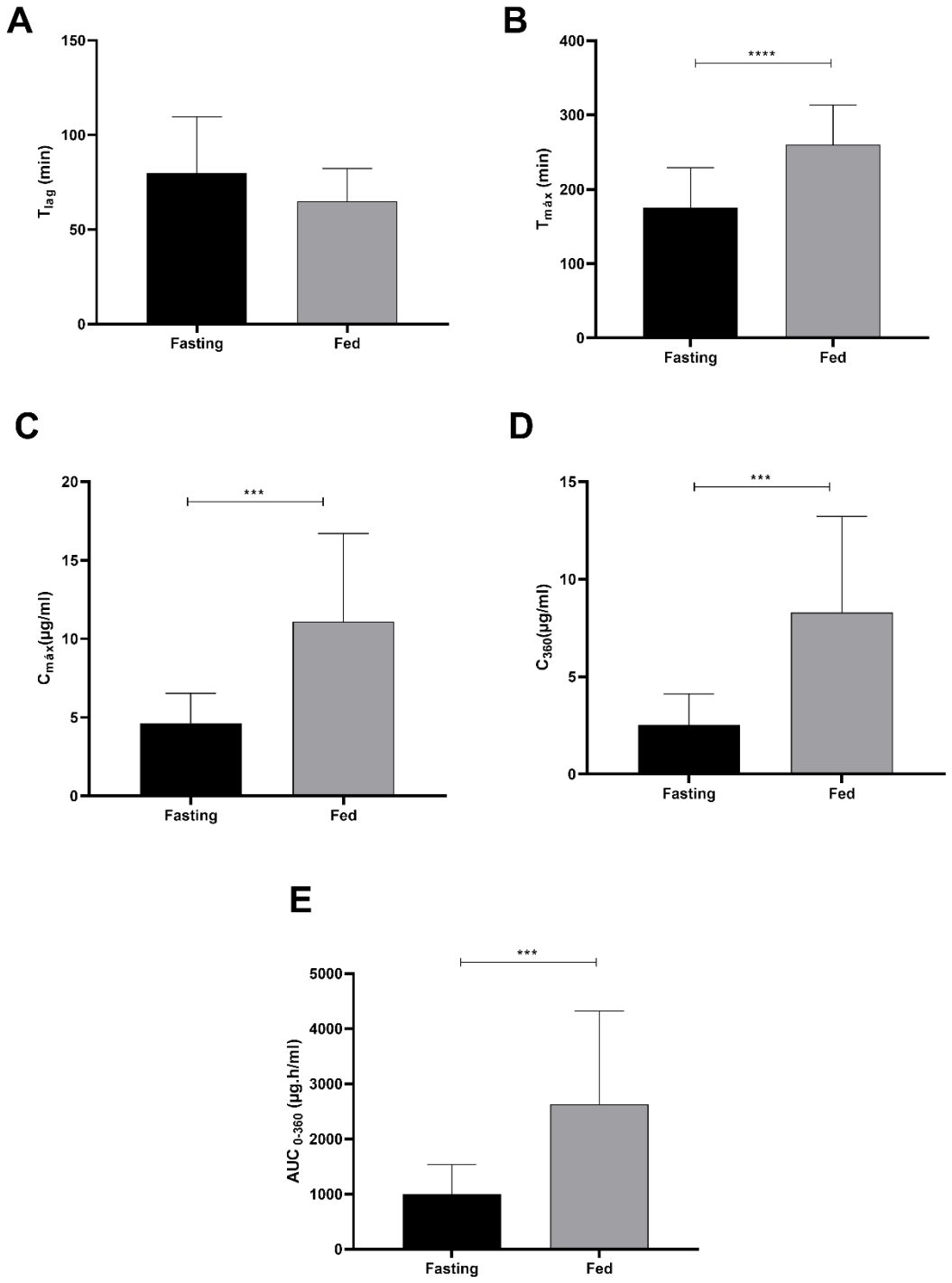

Figure 3. Pharmacokinetics parameters evaluated *in vivo*.(A) the time at which metronidazole first appeared in plasma, (B) -the time it took to reach Cmáx, (C) the highest plasma concentration of metronidazole, (D) the concentration in 6 hours time. (E) the area under the plasma concentration-time curve from time 0 to 360 min. Data are presented as mean ± standard deviation. ***p < 0.001, ****p < 0.0001.

The Table 1 summarizes the gastrointestinal transit and pharmacokinetics parameters obtained for twelve healthy volunteers in both prandial states (fasting and fed). In general, the fasting group presented lower indices of the parameters assessed concerning the fed group.

Table 1. Comparison of the gastrointestinal transit and pharmacokinetic parameters in the group of fasting and fed volunteers. Data are expressed as mean ± SD and median. Different letters indicate statistical differences between groups.

	Fasting									Fed						
Subject	**GRT (min)**	**OCTT (min)**	**SITT (min)**	**FLT (min)**	**T_{lag} (min)**	**$T_{máx}$ (min)**	**$C_{máx}$ (µg/ml)**	**C_{360} (µg/ml)**	**AUC_{360} (µg.h/ml)**	**GRT (min)**	**OCTT (min)**	**SITT (min)**	**FLT (min)**	**T_{lag} (min)**	**$T_{máx}$ (min)**	**$C_{máx}$ (µg/ml)**
1	150	285	135	60	60	120	4.11	1.28	719.68	180	315	135	90	120	240	7.42
2	105	330	225	75	120	180	2.76	1.23	419.73	120	225	105	75	60	300	4.76
3	180	285	105	90	120	120	2.81	1.48	606.78	225	330	105	120	60	240	5.8
4	90	270	180	60	60	120	4.71	2.79	899.46	180	285	105	120	60	240	16.61
5	120	225	105	45	120	240	4.71	1.79	938.67	135	270	135	75	60	240	8.05
6	150	240	90	90	120	240	2.84	0.98	391.92	180	240	60	105	60	360	8.75
7	90	180	90	60	60	240	9.48	5.2	2298.21	150	270	120	75	60	240	20.32
8	90	225	135	60	60	120	6.52	4.66	1450.05	150	270	120	120	60	180	16.27
9	150	270	120	75	60	120	5.21	3.08	1220.7	180	300	120	90	60	240	11.57
10	105	225	120	75	60	180	5.13	4.91	1437.08	135	240	105	90	60	240	19.65
11	90	195	100	45	60	240	3.87	1.19	794.13	120	225	105	60	60	360	6.5
12	120	240	120	75	60	180	3.34	1.81	797.73	180	255	75	120	60	240	7.41
Mean	120[a]	247	127	67[a]	80	175[a]	4.62[a]	2.53[a]	997.85[a]	161[b]	269	107	95[b]	65	260[b]	11[b]
SD	29.37	40.39	37.77	14.36	28.28	51.72	1.83	1.51	513.52	31.42	34.12	22.00	21.53	17.32	53.26	5.62

* GRT- gastric retention time; OCTT - orocecal transit time; SITT – small intestine transit time; FLT- floating lag time; Tlag - the time at which metronidazole first appeared in plasma; Tmáx -the time it took to reach Cmáx; Cmáx - the highest plasma concentration of metronidazole; C360 - the concentration in 6 hours time; AUC0−360, the area under the plasma concentration-time curve from time 0 to 360 min).

Thus, based on the results presented, it is possible to establish an association between the parameters analyzed in the fasted and fed groups (Figure 4). It is observed that the FLT, GRT, and Tmax parameters show a correlation among them, indicating a progressive increase in these parameters, respectively. A larger FLT and GRT provides a larger Tmax.

In the fed state, the FLT was higher due to the increased gastric viscosity, which delayed the tablet's flotation. Therefore, the increase in FLT leads to a prolongation of GRT, which in turn results in an increased Tmax, characteristic of controlled release systems for this gastroretentive system with metronidazole. However, although there is a delay in the time to reach maximum concentration, it also promotes an improvement in bioavailability, as evidenced by the increase in Cmax and AUC parameters in the fed state.

In this context, the correlation between these parameters is relevant in gastroretentive systems, as it highlights the time required to achieve flotation (FLT), which may be a limiting factor for the system's efficacy. In practice, a high FLT can compromise the GRT, especially under fasting conditions, where the risk of early gastric emptying is greater due to the activity of the migrating motor complex (MMC). Thus, in the case of metronidazole, whose efficacy depends on maintaining plasma concentration over time, the pharmacokinetic profile observed here is satisfactory.

In comparison with previously published studies, the results obtained in this work are consistent with the literature. Weitschies et al. (2023) evaluated the *in vivo* behavior of enteric capsules in two prandial states: fasting and fed. The GRT in the fasting state was 43 ± 32 minutes, whereas after meal ingestion (fed state), this time significantly increased to 158 ± 36 minutes.

As for non gastroretentive systems, Cora et al. (2006) investigated HPMC capsules coated with enteric polymer (Eudragit® S100) designed for colonic release. In this study, the GRT was 55 ± 19 minutes, reflecting the rapid gastric transit of the formulation in fasted individuals. In contrast, the data obtained in the present work showed a significantly prolonged GRT in both fasting and fed conditions, supporting the effectiveness of the gastroretentive formulation strategy employed.

Thus, the results and discussion presented show that magnetic data are directly associated with pharmacokinetic data, reinforcing the usefulness of pharmacomagnetography as a complementary tool for non-invasive monitoring of drug biodistribution, retention and release, contributing to a better understanding of the mechanisms of action and therapeutic efficacy of magnetic release systems.

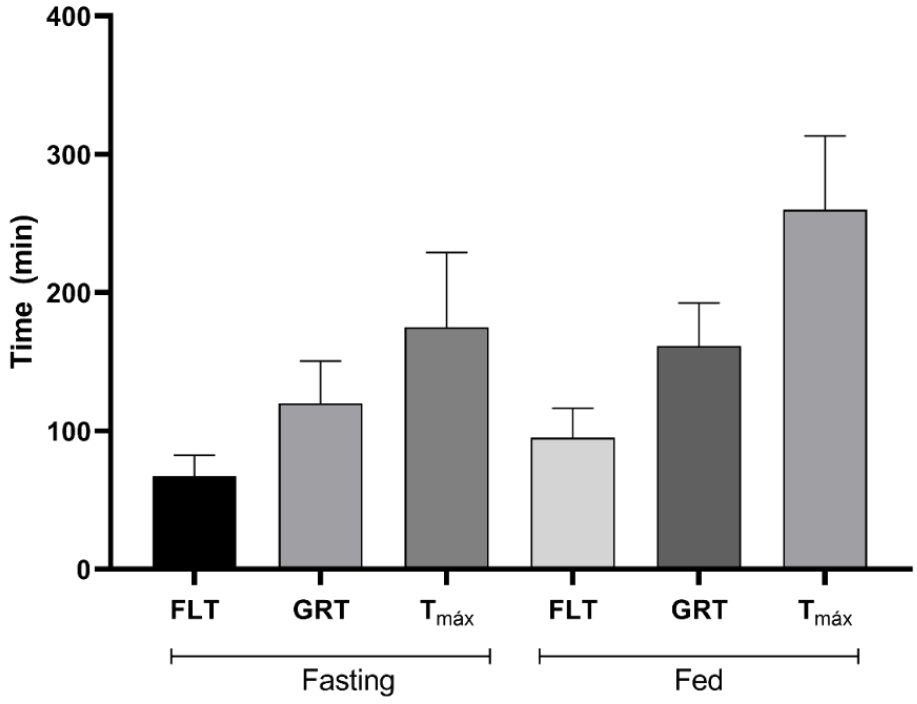

Figure 4. Association between pharmacokinetic parameters and those obtained from pharmacomagnetography in both prandial states: fasting and fed.

4. Conclusion

This study comprehensively investigated the *in vivo* performance of a magnetic floating prolonged-release system (MFDDS) containing metronidazole, using pharmacomagnetography (PMG) based on alternating current biosusceptometry (ACB) to correlate gastrointestinal transit with the pharmacokinetic profile of the drug in healthy volunteers under fasting and fed conditions. The results demonstrated the significant influence of prandial state on MFDDS behavior. It was observed that the presence of food notably prolonged the gastric retention time (GRT) and floating lag time (FLT), attributed to the increased viscosity of gastric contents that delays the initial flotation of the tablet. This extended gastric retention in the fed state translated into more complete and sustained metronidazole absorption, evidenced by significantly higher maximum plasma concentrations ($Cmax$) maintained for a longer period compared to the fasting state, where accelerated gastric emptying limited the absorption window.

The application of pharmacomagnetography proved to be a powerful tool, allowing non-invasive and real-time monitoring of MFDDS location in the gastrointestinal tract and its direct correlation with drug plasma levels, confirming the effectiveness of the gastroretentive system in prolonging metronidazole release in the upper GIT, optimizing its bioavailability. The ACB system enabled real-time monitoring of the gastrointestinal transit of the formulation in volunteers, allowing for precise determination of crucial parameters such as gastric retention time (GRT) and orocecal transit time (OCTT) under different prandial conditions (fasted and fed). By correlating these localization and motility data with the pharmacokinetic profiles of metronidazole, the BAC system was essential in demonstrating how the prandial state influences the behavior of the MFDDS and, consequently, the drug's absorption and bioavailability, validating the effectiveness of the proposed gastroretentive approach.

It is concluded, therefore, that the evaluated MFDDS represents a promising strategy to improve therapy with drugs such as metronidazole, especially when administered after meals, and that the PMG technique provides valuable information for the development and evaluation of gastroretentive drug delivery systems, contributing to the optimization of future pharmaceutical formulations.

APPENDICES

- **NUTRITIONAL INFORMATION OF PROVIDED FOOD**

Del Valle® Orange Juice (200 mL)

Table 1. Nutritional Informatio of Orange Juice

Energy Value (Kcal)	**84**
Carbohydrates (g)	21
Total sugars (g)	21
Added Sugars (g)	14
Sodium (mg)	6,2
Vitamin C (mg)	38

Perdigão® Bolognese Lasagna (600g)

Table 2. Nutritional Information of Lasagna

Energy Value (Kcal)	**684**
Carbohydrates (g)	72
Total sugars (g)	8,4
Added Sugars (g)	0
Proteins (g)	22,2
Tatol Fat (g)	34,2
Satured Fat (g)	13,2
Trans Fat (g)	0
Dietary Fiber (g)	5,4
Sodium (g)	1,68

Perdigão® Pork Ham (40g – 2 slices)

Table 3. Nutritional Information of Ham

Energy Value (Kcal)	**41**
Carbohydrates (g)	0,6
Total Sugars (g)	0,4
Added sugars (g)	0,1
Proteins (g)	6,4
Total Fat (g)	1,2
Satured Fat (g)	0,4
Trans Fat (g)	0

Dietary Fiber (g)	0
Sodium (mg)	451

Seven Boys® Sliced Bread (50g – 2 slices)

Table 4. Nutritional Information of Slced Bread

Energy Value (Kcal)	**127**
Carbohydrates (g)	25
Total Sugars (g)	26
Added Sugars (g)	1,4
Proteins (g)	4,7
Total Fat (g)	0,9
Saturated Fat (g)	0,2
Trans Fat (g)	0
Monounsaturated Fat (g)	0,2
Polyunsatured Fat (g)	0,5
Cholesterol (g)	0
Dietary Fiber (g)	1,6
Sodium (mg)	194

Sadia® Mozzarella Cheese (30g – 2 slices)

Table 5. Nutritional Information of Mozzarella Cheese

Energy Value (Kcal)	**96**
Carbohydrates (g)	0,6
Total Sugars (g)	0,6
Proteins (g)	7,2
Total Fat (g)	7,2
Saturated Fat (g)	4
Sodium (mg)	128
Calcium (mg)	221

- **MAGNETIC REAL-TIME TRACKING, MONITORING, AND IMAGING OF GRDDS IN VIVO IN TWO PRANDIAL STATES**

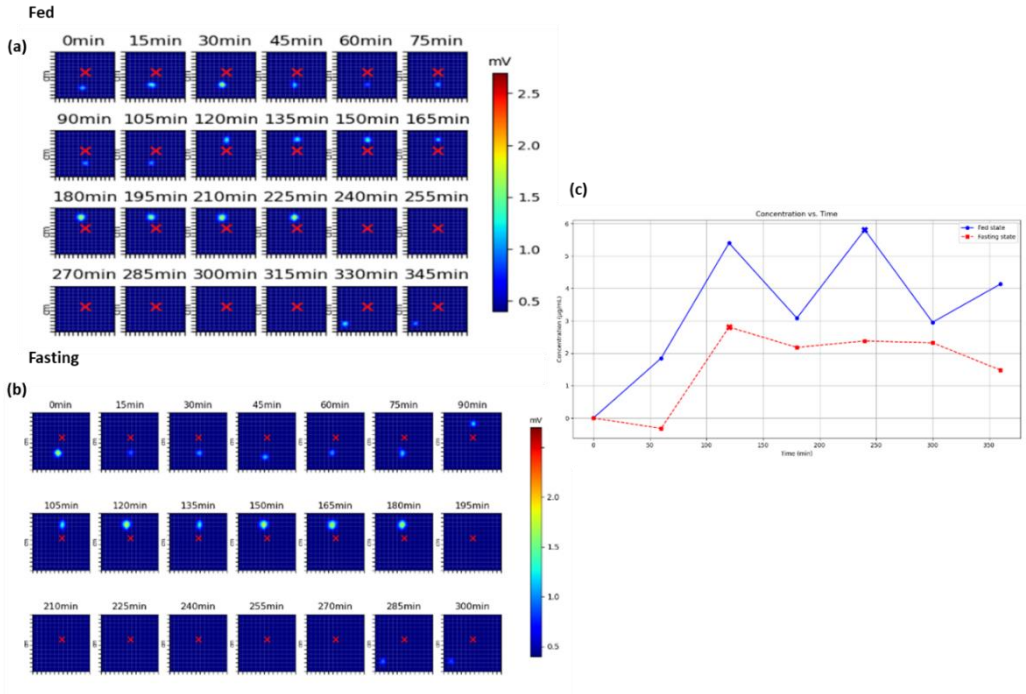

Figure 1. Magnetic real-time tracking, monitoring, and imaging of GRDDS *in vivo* in two prandial states: (A) fed and (B) fasting. The red cross indicates umbilical scar reference. (C) Pharmacokinetic analysis showing drug concentration over time (pharmacokinetics) in both prandial states (fed - blue line, fasted - red line).

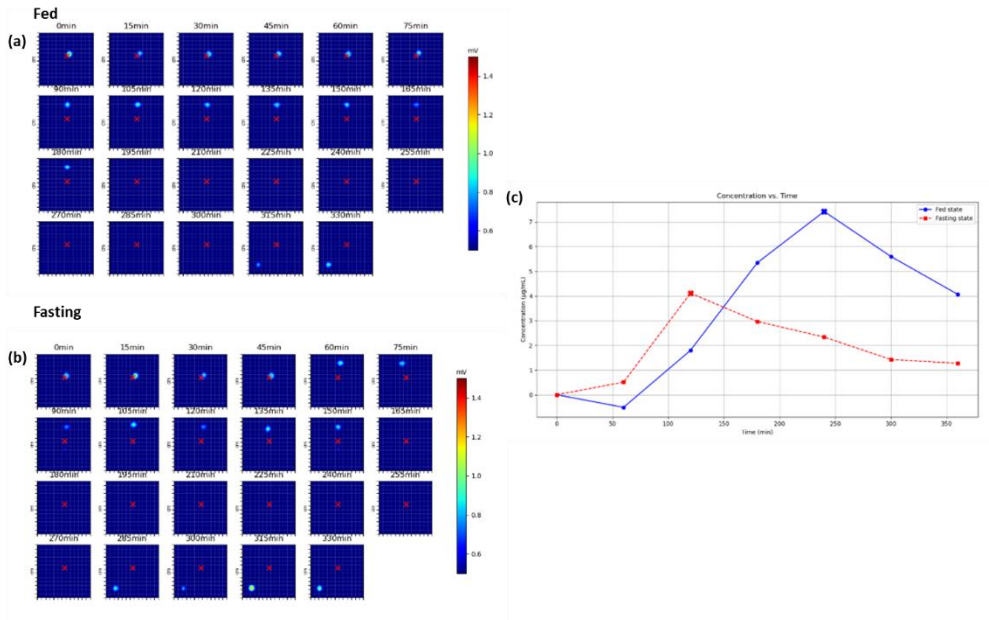

Figure 2. Magnetic real-time tracking, monitoring, and imaging of GRDDS *in vivo* in two prandial states: (A) fed and (B) fasting. The red cross indicates umbilical scar reference. (C) Pharmacokinetic analysis showing drug concentration over time (pharmacokinetics) in both prandial states (fed - blue line, fasted - red line).

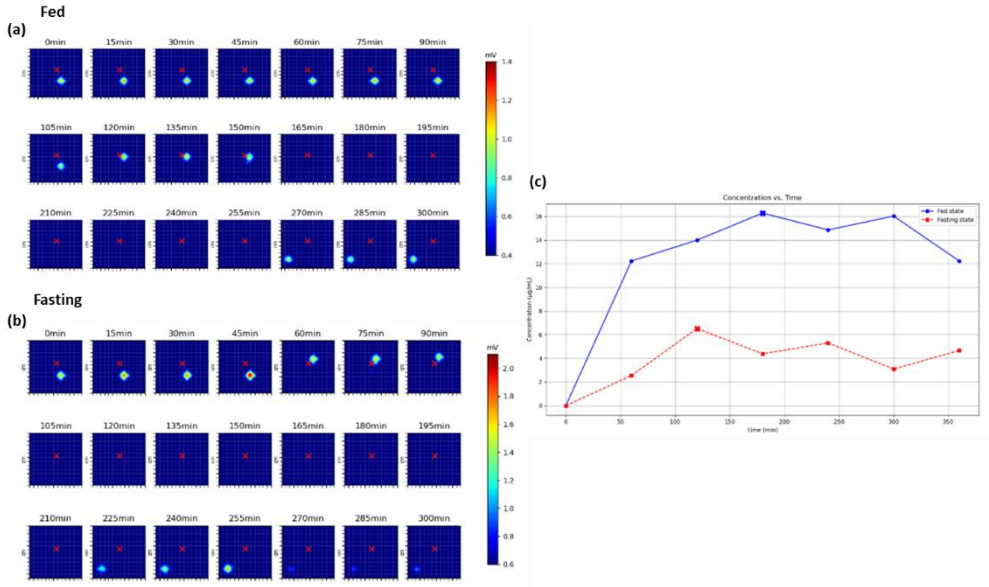

Figure 3. Magnetic real-time tracking, monitoring, and imaging of GRDDS *in vivo* in two prandial states: (A) fed and (B) fasting. The red cross indicates umbilical scar reference. (C) Pharmacokinetic analysis showing drug concentration over time (pharmacokinetics) in both prandial states (fed - blue line, fasted - red line).

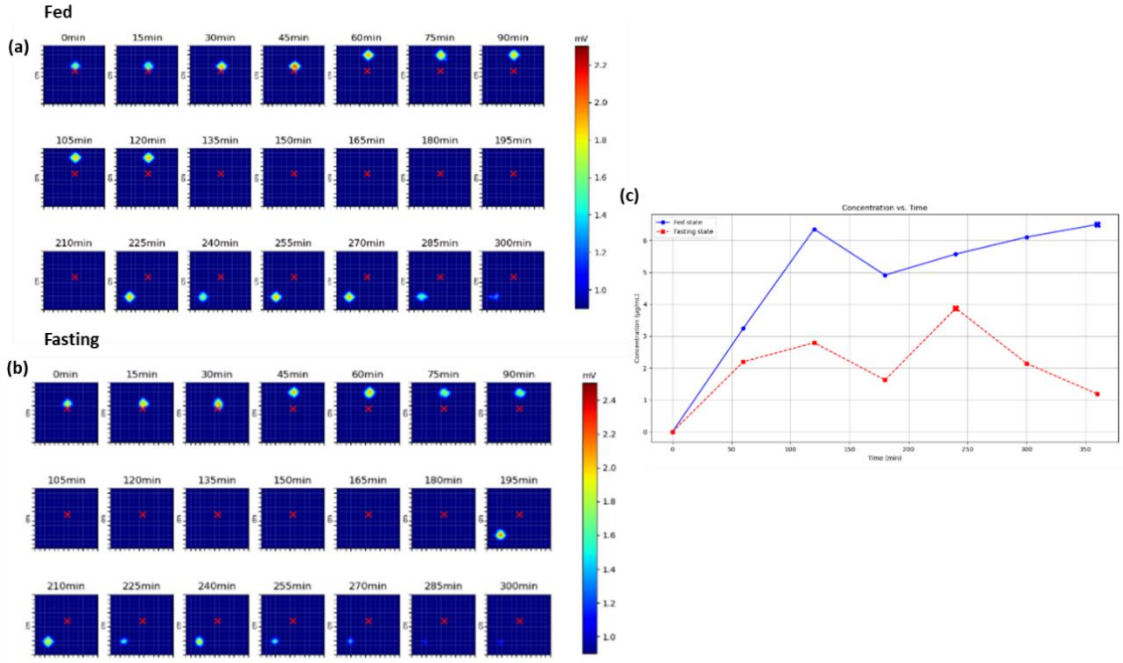

Figure 4. Magnetic real-time tracking, monitoring, and imaging of GRDDS *in vivo* in two prandial states: (A) fed and (B) fasting. The red cross indicates umbilical scar reference. (C) Pharmacokinetic analysis showing drug concentration over time (pharmacokinetics) in both prandial states (fed - blue line, fasted - red line).

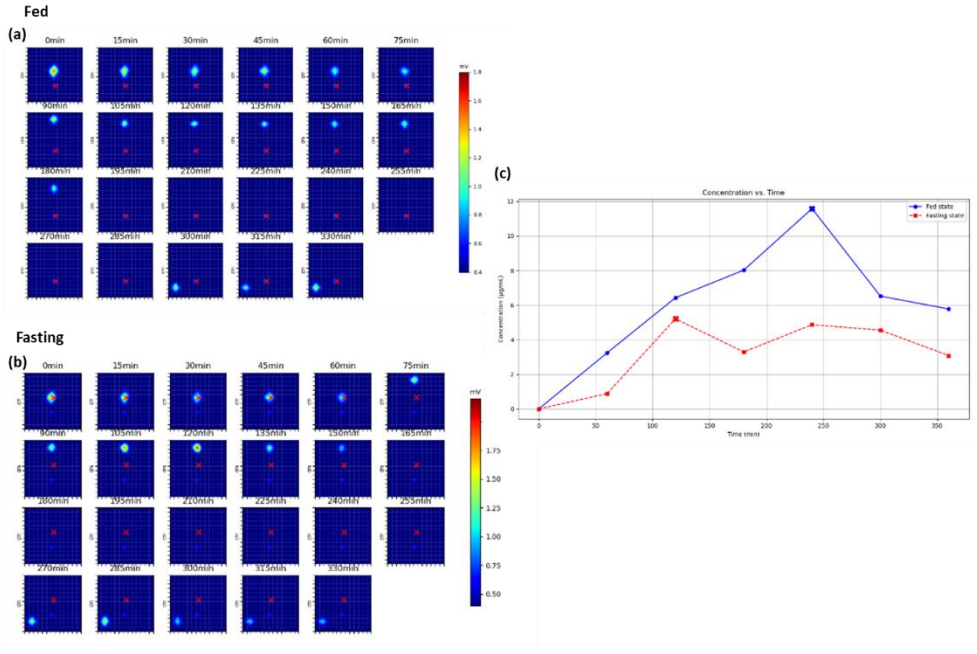

Figure 5. Magnetic real-time tracking, monitoring, and imaging of GRDDS *in vivo* in two prandial states: (A) fed and (B) fasting. The red cross indicates umbilical scar reference. (C) Pharmacokinetic analysis showing drug concentration over time (pharmacokinetics) in both prandial states (fed - blue line, fasted - red line).

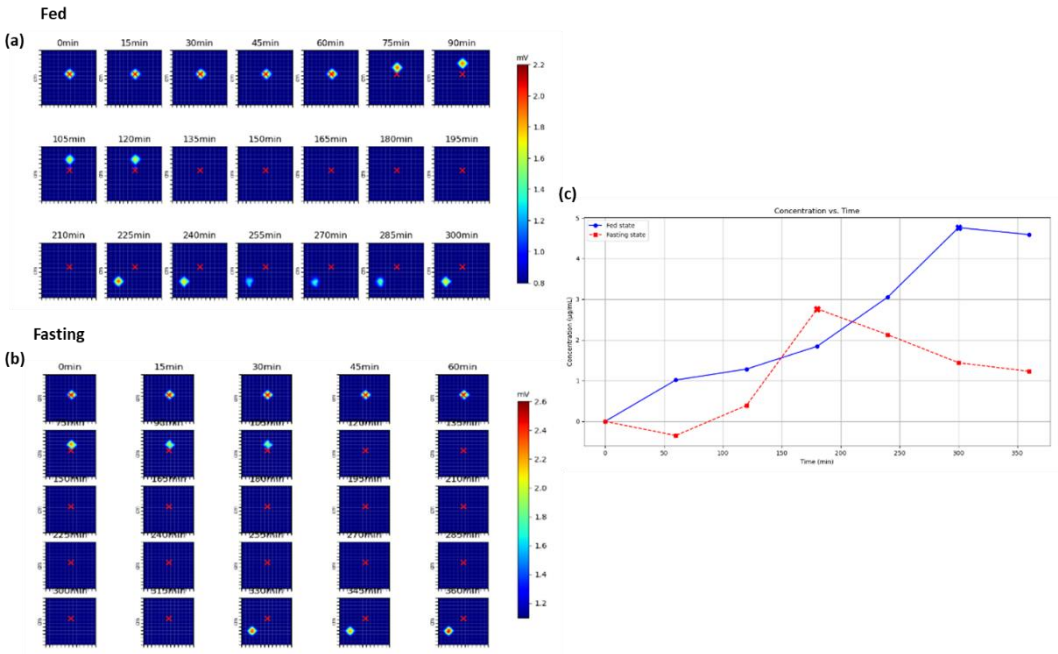

Figure 6. Magnetic real-time tracking, monitoring, and imaging of GRDDS *in vivo* in two prandial states: (A) fed and (B) fasting. The red cross indicates umbilical scar reference. (C) Pharmacokinetic analysis showing drug concentration over time (pharmacokinetics) in both prandial states (fed - blue line, fasted - red line).

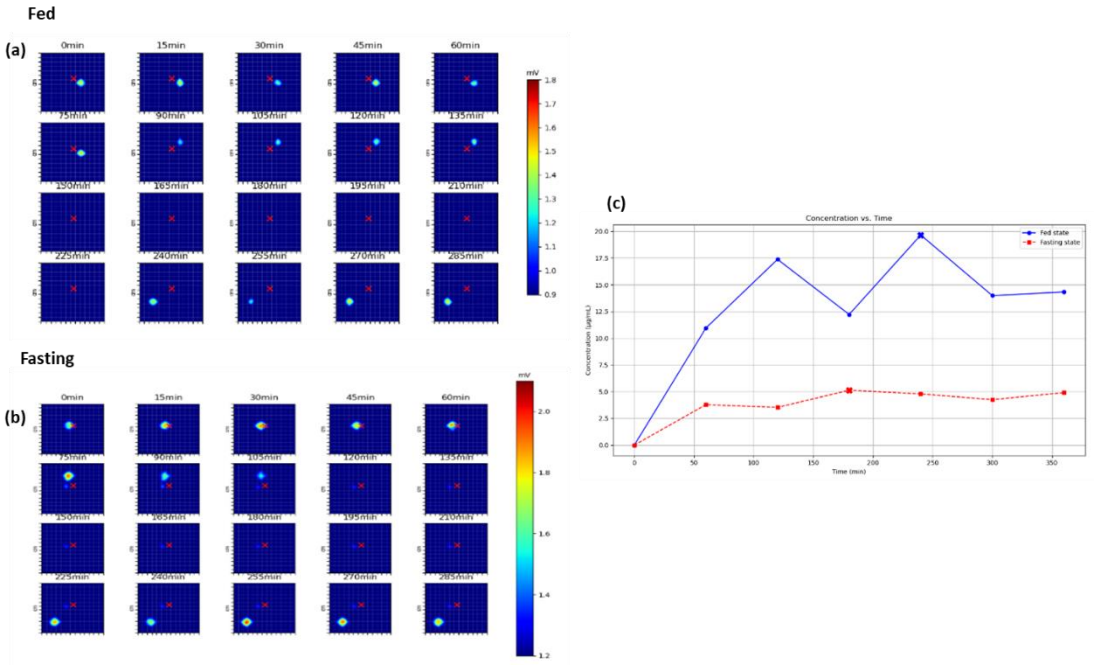

Figure 7. Magnetic real-time tracking, monitoring, and imaging of GRDDS *in vivo* in two prandial states: (A) fed and (B) fasting. The red cross indicates umbilical scar reference. (C) Pharmacokinetic analysis showing drug concentration over time (pharmacokinetics) in both prandial states (fed - blue line, fasted - red line).

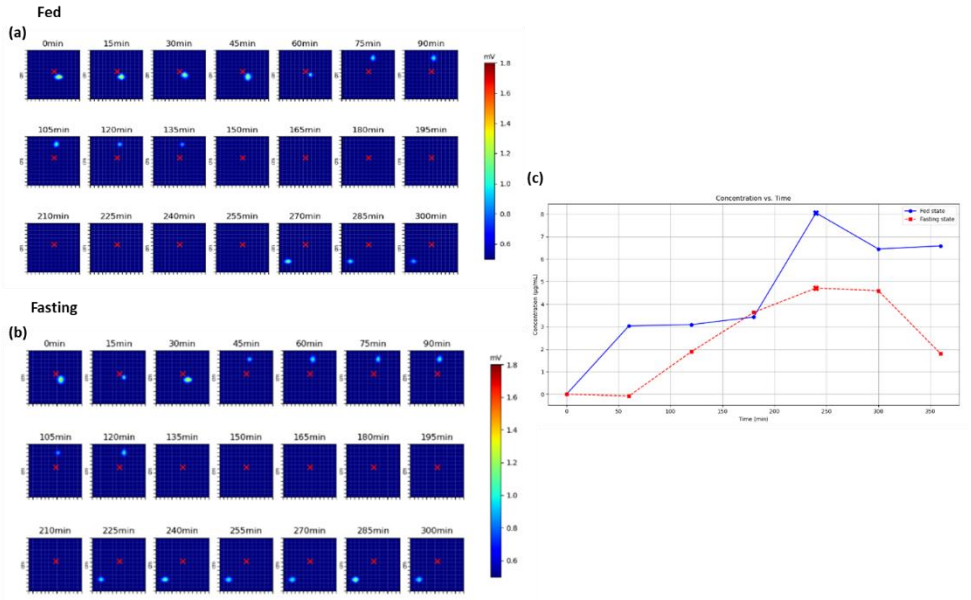

Figure 8. Magnetic real-time tracking, monitoring, and imaging of GRDDS *in vivo* in two prandial states: (A) fed and (B) fasting. The red cross indicates umbilical scar reference. (C) Pharmacokinetic analysis showing drug concentration over time (pharmacokinetics) in both prandial states (fed - blue line, fasted - red line).

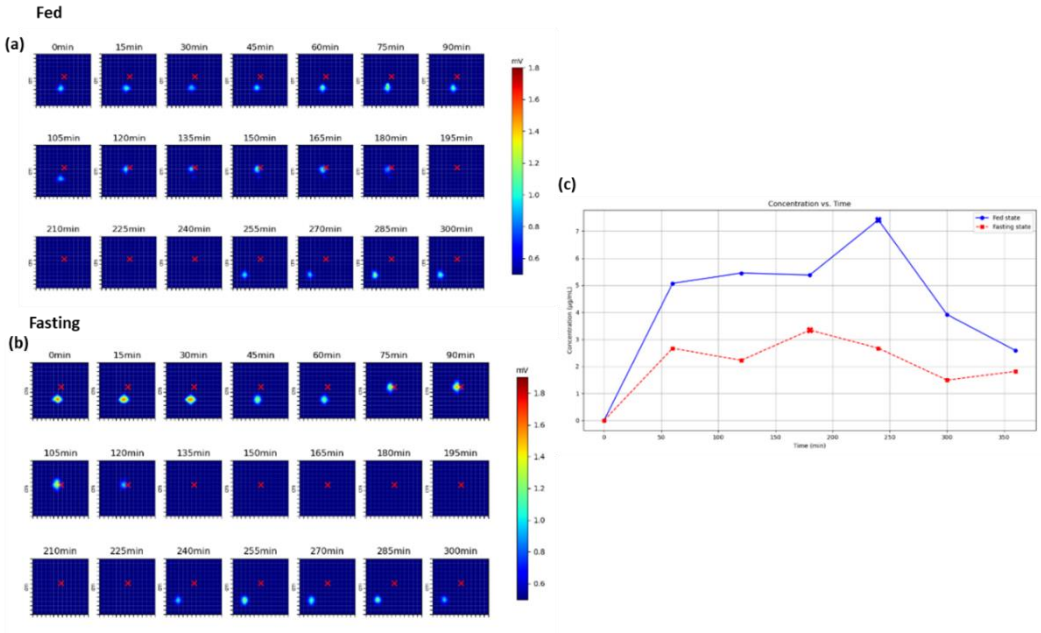

Figure 9. Magnetic real-time tracking, monitoring, and imaging of GRDDS *in vivo* in two prandial states: (A) fed and (B) fasting. The red cross indicates umbilical scar reference. (C) Pharmacokinetic analysis showing drug concentration over time (pharmacokinetics) in both prandial states (fed - blue line, fasted - red line).

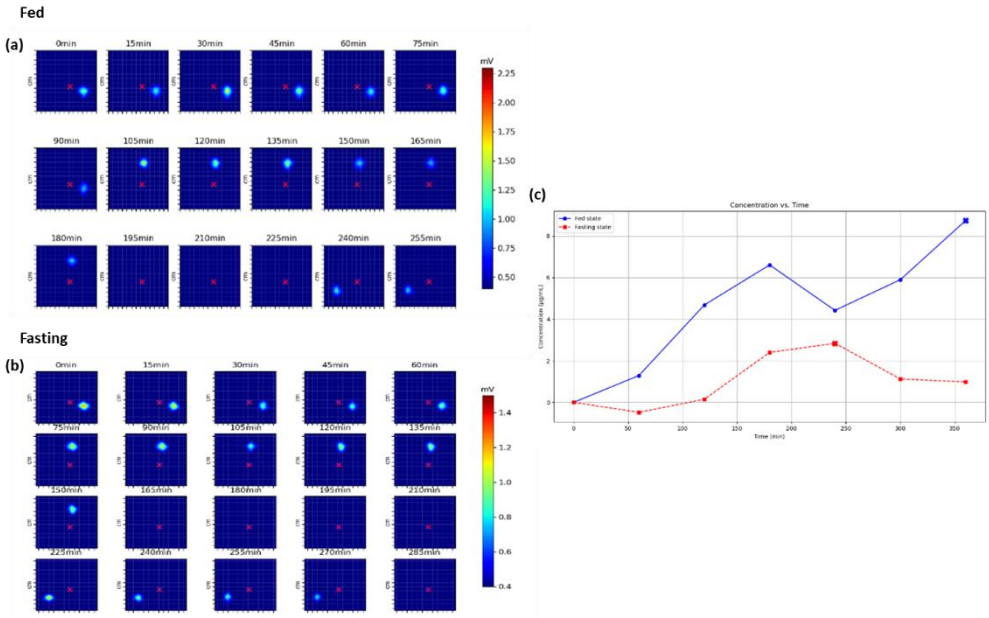

Figure 10. Magnetic real-time tracking, monitoring, and imaging of GRDDS *in vivo* in two prandial states: (A) fed and (B) fasting. The red cross indicates umbilical scar reference. (C) Pharmacokinetic analysis showing drug concentration over time (pharmacokinetics) in both prandial states (fed - blue line, fasted - red line).

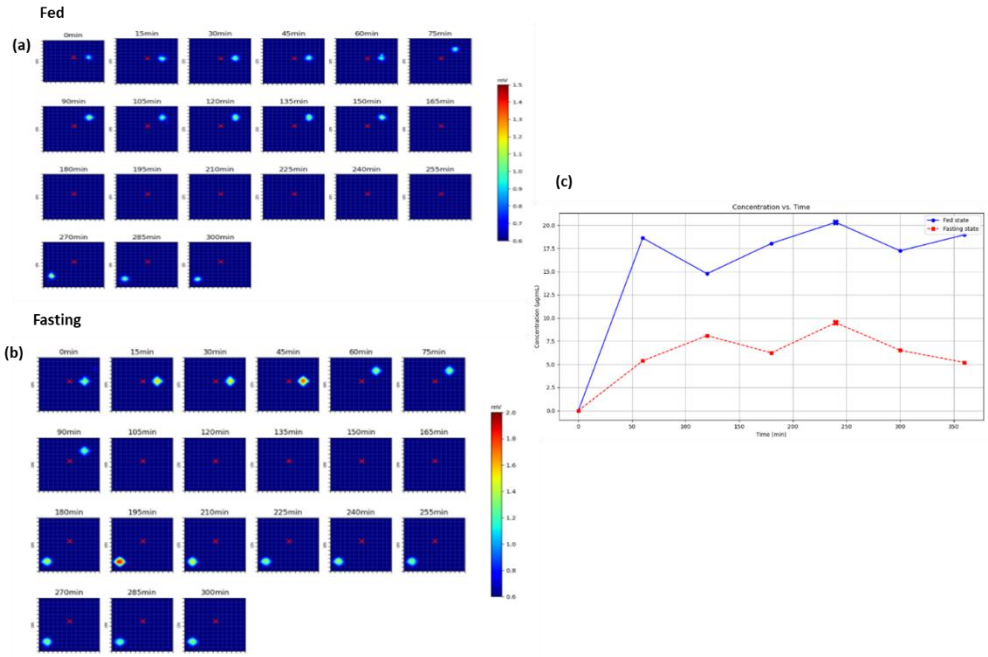

Figure 11. Magnetic real-time tracking, monitoring, and imaging of GRDDS *in vivo* in two prandial states: (A) fed and (B) fasting. The red cross indicates umbilical scar reference. (C) Pharmacokinetic analysis showing drug concentration over time (pharmacokinetics) in both prandial states (fed - blue line, fasted - red line).

Figure 11. Magnetic real-time tracking, monitoring, and imaging of GRDDS *in vivo* in two prandial states: (A) fed and (B) fasting. The red cross indicates umbilical scar reference. (C) Pharmacokinetic analysis showing drug concentration over time (pharmacokinetics) in both prandial states (fed - blue line, fasted - red line).

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CONCLUSÃO GERAL

O presente estudo demonstrou de forma clara e consistente a eficácia de um sistema de liberação prolongada gastroretentivo flutuante magnético (MFDDS) contendo metronidazol como fármaco modelo, avaliando seu desempenho tanto *in vitro*, em diferentes condições físico-químicas, quanto *in vivo*, sob distintos estados prandiais (jejum e alimentado), por meio da técnica de farmacomagnetografia associada à biossusceptometria de corrente alternada (BAC). Os ensaios *in vitro* permitiram uma avaliação detalhada do comportamento das MFDDS frente a diferentes cenários fisiológicos simulados (pressão intragástrica e viscosidade do meio). Observou-se que o aumento da viscosidade do meio e da pressão aplicada retardou significativamente o início da flutuação (FLT) dos comprimidos. Esse comportamento está diretamente relacionado à menor taxa de difusão de água para o interior da matriz polimérica, resultando em um processo mais lento de intumescimento do hidrogel (HPMC) e, consequentemente, na liberação retardada de gás carbônico mecanismo essencial para a redução da densidade e aquisição da flutuabilidade. Os resultados *in vitro* foram validados de maneira robusta nos estudos *in vivo*, realizados com voluntários sob condições de jejum e alimentado, os quais confirmaram a influência desses parâmetros sobre o desempenho do sistema no trato gastrointestinal. No estado alimentado, caracterizado por maior viscosidade e menor motilidade, foi observado um aumento expressivo do FLT, acompanhado de um prolongamento significativo do tempo de retenção gástrica (GRT) e do tempo de trânsito orocecal (OCTT). Esse comportamento favoreceu uma liberação controlada e sustentada do metronidazol, traduzida em maiores valores de Cmax e AUC, quando comparados aos resultados obtidos na condição de jejum, onde o esvaziamento gástrico acelerado, manteve por menos tempo o metronidazol exposto aos sítios de absorção, consequentemente diminuindo a concentração no plasma ao longo do tempo.

O cruzamento dos dados obtidos *in vitro* e *in vivo* reforça a consistência do modelo experimental adotado e evidencia que a simulação de parâmetros fisiológicos, como viscosidade e pressão, é essencial para prever o comportamento real das formas gastroretentivas no trato gastrointestinal humano. A similaridade nos efeitos observados em ambos os contextos confirma que o aumento da viscosidade seja por simulação laboratorial ou pela presença de alimento exerce papel fundamental no retardo da flutuação e na extensão da retenção gástrica. A aplicação da farmacomagnetografia, associada à técnica BAC, foi de grande importância para validar esses resultados, destacando-se como uma ferramenta inovadora e não invasiva capaz de monitorar, em tempo real, a localização do MFDDS no trato gastrointestinal e correlacionar diretamente esses dados de trânsito com os perfis farmacocinéticos do fármaco. Esta abordagem permitiu não apenas acompanhar os parâmetros de motilidade gastrointestinal (FLT, GRT e OCTT), mas também compreender como essas variáveis impactam diretamente a liberação e absorção do fármaco. Portanto, os dados obtidos neste estudo comprovam que os comprimidos magnéticos flutuantes avaliados constituem uma estratégia altamente eficaz e promissora para otimizar a terapia com fármacos que possuem janela de absorção restrita no trato gastrointestinal superior, como é o caso do metronidazol, especialmente quando administrados após as refeições. Por fim, as perspectivas futuras incluem a ampliação da aplicação da farmacomagnetografia para outras classes de formas farmacêuticas gastroretentivas (flutuantes, expansíveis, bioadesivas ou magnéticas), bem como a utilização desta metodologia como ferramenta padrão no desenvolvimento e na

validação de sistemas de liberação controlada, contribuindo significativamente para a inovação tecnológica na área farmacêutica.